**Dwight D. Eisenhower Army Medical Center (DDEAMC)**

**Human Research Protection Program (HRPP)**

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# Chapter 1: Framework

## 1.1 Background

The Dwight D. Eisenhower Army Medical Center (DDEAMC) has a long-standing reputation as one of the finest teaching institutions in the Army Medical Department (AMEDD). A fundamental mission of DDEAMC is to train physicians, dentists, other healthcare professionals and a variety of allied health disciplines for service to the Army and the nation. A critical part of this training includes the conduct of high quality basic science and clinical research in conjunction with the organization's goal of providing the best patient care possible. DDEAMC recognizes and affirms the need for academic freedom in the conduct of research, and the value of well-designed, responsible investigative activities that involve human subjects. At the same time, DDEAMC recognizes its responsibility in the area of human subjects and is committed to protecting the rights and welfare of subjects in human research conducted under its Assurances for the protection of human subjects. The use of human subjects in research or investigational activities imposes both ethical and legal responsibilities upon this organization, its leadership, and staff; principal investigators (PIs); associate investigators (AI), residents, student researchers, and other researchers; research team members; and everyone else involved in research endeavors for assuring that the welfare and rights of human subjects are adequately protected.

Research activities conducted at DDEAMC and the military treatment facilities (MTFs) covered under its Assurances encompass investigator-initiated research, directed research, collaborative studies, and multi-institutional clinical trials. The research involves a broad spectrum of studies, including applied research, basic science research, behavioral studies, healthcare delivery evaluations, educational outcome studies, development and testing of drugs, devices, diagnostics, and epidemiological studies.

## 1.2 Plan

The DDEAMC will work within a systematic human research protection program (HRPP) designed to ensure the rights, safety, and well being of human research subjects participating in research activities conducted under its Assurances. The physical resources and support staff are provided through DDEAMC. A comprehensive system of rules, documents, policies and procedures, processes, and people whose mission is to protect human subjects are the primary parts of the DDEAMC HRPP. This document is part of the effort to ensure that an ethical research environment is supported by including accountability, adequate resources, ethics education training, transparency, and open communication. The Department of Clinical Investigation (DCI) was charged with the full implementation of this plan to include policy origination, maintenance, education and training, communication and ongoing monitoring of this HRPP. The DCI Research Regulatory Compliance Office (RRCO) is responsible for the development, documentation and maintenance of the HRPP and is physically located at 7$^{th}$ Alley, Building 38711, Fort Gordon, Georgia, 30905.

## 1.3 Assurances

### Background Information

The Common Rule requires that every institution engaged in non-exempt federally supported human subject research file an "Assurance" to formalize its commitment to the protection of human subjects [32 CFR 219.103(a)]. The DDEAMC must provide written assurance to federal agencies that it will comply with all federal laws and regulations governing the protection of human research subjects.

The DoD requires that any DoD institution which conducts or engaged in non-exempt research involving human subjects hold a current DoD Assurance. For Army institutions, DoD assurances are granted by the Army Assistant Surgeon General for Force Projection.

DoD also requires that DoD institutions which support any research involving human subjects maintain a Human Research Protection Program (HRPP). The assurances are integral to the Human Research Protection Program, as is this HRPP Plan.

The procedures for implementing DDEAMC's assurances and HRPP are provided in this HRPP Plan and referenced documents.

The terms of DDEAMC's HRPP Plan apply whenever the organization supports or becomes engaged in human subject research, even if the research is otherwise exempt from the requirements of the Common Rule.

The DDEAMC holds two Assurances as noted in the following paragraphs.

**Department of Defense (DoD) Assurance A10015**

The DDEAMC holds a Department of Defense (DoD) Assurance for the Protection of Human Research Subjects (DoD A10015). The Commander serves as the Institutional Official (IO) for the Assurance, and the Human Research Protections and Compliance Administrator serves as the Human Protections Administrator (HPA). Whenever there is a change in the IO, the Assurance of Compliance will be renewed through the Army Human Research Protection Office (AHRPO). The HPA will notify AHRPO of an upcoming change in the IO at least 90 days before the change, so there will be enough time to conduct a review of the DDEAMC HRPP before the new IO is in place.

Whenever there is a significant change to the DDEAMC HRPP—such as a change in HPA, new policies or procedures, new Institutional Agreements (IA) for Institutional Review Board (IRB) Review, or new Memos of Agreement or Understanding (MOA or MOU) —notice of the change, together with a copy of the new documents, as applicable, will be sent to AHRPO for the official Assurance file. Before a new HPA can be assigned, the prospective HPA must complete the required education and training, and must complete a robust turnover with the outgoing HPA to ensure a complete and careful transition of duties and responsibilities for the protection of human subjects.

To maintain its DoD Assurance, DDEAMC will:

1. Submit initial reports of serious and continuing noncompliance to AHRPO when reported to the DDEAMC IRB or HPA. A final report shall be submitted as soon as the investigation has been completed.

2. Submit an annual report to AHRPO prior to the anniversary date of the Assurance. The annual report will include, but is not limited to, the following:
    a. Updates to satisfy the Assurance and HRPP approval requirements;
    b. Updated HRPP plan;
    c. Changes in key HRPP staff or their responsibilities;
    d. Adequacy of resources to meet the current workload;
    e. Summary of reports of non-compliance for prior year, to include a general description of the incident, specific allegations, summary of the investigation completed, description of the findings and outcome, and changes implemented; and,
    f. Description of quality improvement and compliance activities conducted over the prior year.

**Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) Federal Wide Assurance (FWA) 00004975**

The DDEAMC holds a Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) Federal Wide Assurance (FWA) (FWA # 00004975). As with the DoD Assurance, the Commander serves as the Institutional Official (IO) for the Assurance, and the Human Research Protections and Compliance Administrator serves as the Human Protections Administrator (HPA). Whenever there is a change in the IO, the FWA will be renewed through the DHHS OHRP as outlined on their website (http://www.hhs.gov/ohrp/assurances/assurances_index.html).

Whenever there is a significant change to the DDEAMC HRPP—such as a change in HPA, new policies or procedures, new Institutional Agreements for Institutional Review Board (IRB) Review, or new Memos of Agreement or Understanding (MOA or MOU) for sites — the FWA will be updated promptly.

## 1.4 Components and Facilities Covered by the HRPP

All proposed human subjects research conducted under DDEAMC's Assurances of DoD A10015 and DHHS OHRP FWA #00004975, unless deemed exempt by the DDEAMC IRB in accordance with Title 32 Code of Federal Regulations (CFR) 219.101 and 45 CFR 46.101, is subject to the terms of this HRPP.

**Facilities Covered by this HRPP**

The following facilities are covered by this HRPP to include:

- Dwight D. Eisenhower Army Medical Center, Fort Gordon, GA
    - Rodriquez Army Health Clinic, Fort Buchanan, PR
    - USA Health Clinic, SOUTHCOM, Miami, FL
    - Camp Shelby, MS
- Moncrief Army Community Hospital, Fort Jackson, SC
- Blanchfield Army Community Hospital, Fort Campbell, KY
- Winn Army Community Hospital, Fort Stewart, GA

- Martin Army Community Hospital, Fort Benning, GA
- Lyster Army Health Clinic, Fort Rucker, AL
- Fox Army Health Clinic, Redstone Arsenal, AL

## 1.5 Goal and Objectives of the HRPP

### HRPP Goal

The goal of the HRPP is to assure that all human subject research conducted in DDEAMC and all of the military treatment facilities (MTF) under its Assurances are guided by the ethical principles set forth in the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (The Belmont Report). This HRPP will ensure that all covered research activities:

- Recognize the rights and welfare of human research subjects and ensure that these rights are maintained and protected,

- Are guided by the ethical principles of respect for persons, beneficence, and justice as set forth in The Belmont Report, and are conducted with the highest level of expertise and integrity, and

- Comply with applicable federal, DoD, Army, and other laws, and regulations pertaining to the protection of human research subjects such as the Department of Defense, Title 32 Code of Federal Regulations (CFR) 219, Protection of Human Subjects; Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research";* Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP) for the Protection of Human Subjects in Title 45 CFR 46 including subparts A, B, C, D, E; and the Food and Drug Administration (FDA) Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56.

### HRPP Objectives

The objectives of the HRPP are to outline specific policies and procedures that implement the organization's Assurances and to ensure ongoing compliance with DoD, Army, and federal regulations, laws, and policies for human subjects protection. More specifically objectives include:

- Outline specific policies and procedures for the required scientific, regulatory, and ethical review and approval of research using human subjects.

- Establish and direct initial and continuing education requirements for personnel involved in research using human subjects.

- Assign roles and responsibilities for the HRPP.

- Ensure maintenance of necessary documentation and records.

- Ensure accurate and comprehensive transition of HRPP responsibilities and duties when there is a change in the DDEAMC IO, IRB Chair, or HPA.

## 1.6 Activities Covered by the HRPP

Research involving human subjects must be conducted under a comprehensive program that ensures compliance with federal, DoD, and Department of the Army (DA) laws and regulations for the protection of the rights, safety, and well-being of all individuals involved.

All research involving human subjects that is supported in whole or in part by DDEAMC or its affiliated institutions must comply with this HRPP.

All non-exempt research conducted by DDEAMC or its affiliated institutions must comply with this HRPP and the terms of the DoD Assurance A10015 and

Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) Federal Wide Assurance (FWA) #00004975.

DDEAMC and its affiliates are providing support for research involving human subjects when one or more of these institutions is providing at least some of the resources for the research. Resources may include but are not limited to funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by a non-DoD institution. See DoDI 3216.02, glossary.

DDEAMC and its affiliates are engaged in or conducting non-exempt for research involving human subjects when its personnel are conducting activities covered by section 32 CFR 219.101(a). An institution that is funding, providing equipment, providing access to or information about potential human subjects (but not recruiting human subjects), providing data or specimens (either identifiable or not), or overseeing the research from a regulatory or compliance standpoint is not engaged in the research involving human subjects (but is supporting the research. See DoDI 3216.02, glossary.)

Determining when activities meet the federal definitions of research involving human subjects is not always easy or straightforward. The following definitions are provided IAW with DoDI 3216.02:

> Research involving human subjects. Activities designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects).
>
> The following activities conducted or supported by the Department of Defense are NOT research involving human subjects:

Activities carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease in Service members and other mission essential personnel under force health protection programs of the Department of Defense, including health surveillance pursuant to section 1074f of Reference (g) and the use of medical products consistent with DoD Instruction 6200.02 (Reference (x)).

Authorized health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment.

Activities performed for the sole purpose of medical quality assurance consistent with section 1102 of Reference (g) and DoDD 6025.13 (Reference (y)).

Activities performed solely for an OT&E project where the activities and project meet the definition of OT&E as defined in section 139(a)(2)(A) of Reference (g).

Activities performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units, including such activities as occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information.

Activities, including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of Government officials responsible for the operation or oversight of the program being evaluated and are not intended for generalized use beyond such program.

Survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by DoDD 5240.01 (Reference (z)).

Under DDEAMC's Assurances, it is the responsibility of the DDEAMC IRB Chair or convened board and the HPA to determine what activities constitute research involving human subjects as defined by federal regulations, and whether the organization is supporting the research activity or if the organization is engaged in research. These questions must be answered in order to determine whether an activity is subject to DDEAMC's HRPP:

1. Is the activity research? If no, this HRPP does not apply. Stop here.
2. Does the activity involve human subjects? If no, this HRPP does not apply. Stop here.
3. Is the activity supported by DDEAMC or its affiliates? If yes, this HRPP applies. If no, this HRPP does not apply. Stop here.
4. What specific support is being provided, by whom, when, and how? Does this support include engagement by DDEAMC in the conduct of the research?
   If no, contact the HPA to provide notification of the planned activity and to facilitate institutional requirements, such as regulatory compliance review, command approval, and identification of appropriate points of contact. In some instances, the Army

Human Research Protections Office (AHRPO) may be responsible for the DOD compliance review IAW with the DOD Instruction 3216.02.
If yes, is the research exempt from 32 CFR 219?

If no, both this HRPP and the Federal and DOD Assurances apply.
If yes, this HRPP applies.

Whether or not the research is exempt from 32 CFR 219, HIPAA compliance is required if protected health information will be used or disclosed.

**Defining Research**

The following definitions are taken from the Common Rule[1] (32 CFR 219.102) and are noted below:

"Research" is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities (32 CFR 219.102).

The term "research" designates an activity designed to test a hypothesis or permit conclusions to be drawn and, thereby, to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).

A "systematic approach" involves a predetermined method for researching a specific topic or answering a specific question.

Activities that are normally considered "systematic investigations" include:

- Observational studies
- Interviews (including focus groups) or survey studies
- Group comparison studies
- Program evaluation
- Interventional research
- Some pilot projects

Activities that would **NOT** normally be considered systematic investigations include:

- Training activities (e.g., humans being trained to perform a certain technique, such as marksmanship);

[1] The Common Rule is the Federal Policy for the Protection of Human Subjects, which governs research with human subjects conducted or supported by 17 federal departments and agencies including the DoD. The DoD's codification of the Common Rule is at Title 32 Code of Federal Regulations part 219. The Department of Health and Human Services is the proponent agency of the policy and incorporated it into its code at 45 CFR Part 46, Subpart A.

- Activities involving humans where the objective of the activity is to teach proficiency in performing certain tasks or using specific methods.
- "The term "research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective. . . . The general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects."
- Contributing to generalizable knowledge may be demonstrated by the publication of the results (or conclusions) of the activity, when accompanied by an intent to extend the results beyond a single individual or program; but this is not an exclusive "test". Quality assessment (QA) or quality improvement (QI) projects, where the intention is not to share results beyond the institution or program, are usually ***not*** research activities. (See DoDI 3216.02, glossary, definition of "research involving human subjects" for further information on this topic.) In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal purposes lead to a desire to disseminate the results for application outside the program), the research use of the data collected for another purpose must be reviewed by the IRB.

**Defining "Human Subjects"**

Under The Common Rule (32 CFR 219.102(f)), a "human subject" is a living individual about whom an investigator (whether professional or student) conducting research obtains:

- Data through intervention or interaction with the individual, or
- Identifiable private information. NOTE: The terms "subject" or "participant" are often used interchangeably.

**Obtaining:** Receiving or accessing identifiable private information or identifiable specimens for research purposes. Obtaining includes when an investigator uses, studies, or analyzes, for research purpose, identifiable private information or identifiable specimens already in the possession of the investigator.

**Intervention:** Includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

**Interaction:** Includes interpersonal contact, surveys, or other forms of communication between investigator and subject.

**Individually identifiable:** The identity of the subject is or may readily be ascertained by the investigator or associated with the information. In general, this refers to information or specimens that can be linked to specific individuals directly or indirectly through context, triangulation of data or coding systems.

**Private information:** Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the

individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

**Food and Drug Administration Information**

The FDA has additional clarifications and definitions for terms used in human subjects research. Although there are many similarities, there may be subtle differences that require additional regulatory education, guidance or compliance. Refer to Chapter 5, FDA Regulated Research for additional information.

- DODI 3216.02 states human subjects may be:
- DoD personnel. DoD civilian employees and military services members.
- DoD civilian employee. An individual meeting the definition of "employee" consistent with section 2105 of Reference (m). It includes employees of DoD Non-Appropriated Fund Instrumentalities; DoD civilian employees filling full-time, part-time, intermittent, or on-call positions; and individuals serving under personal services contracts consistent with section 2.101 of Reference (n). It excludes employees of contractors (other than personal services contractors) and foreign nationals of host countries.

1. Service members. Individuals appointed, enlisted, or inducted for military service under the authority of the Department of Defense. The Military Services are the Army, the Navy, the Air Force, the Marine Corps, the Coast Guard, and the Reserve Components, which includes the Army and the Air National Guards of the United States. Members of the Reserve Components are included when in a duty status.

2. Beneficiaries. Retirees and applicable family members.

3. Civilians. Individuals who do not meet the definitions noted above.

**Defining "Human Subject Research"**

Combining these definitions, "human subject research" includes:

- Any activity in which an investigator intervenes or interacts with a human subject, or
- Obtains individually identifiable private information about a human subject in a systematic investigation designed to develop or contribute to generalizable knowledge.

Examples of "research" involving "human subjects," include:

- Testing of drugs, medical devices, or products developed through research;
- Collection of data through *intervention* or *interaction* with individuals;
- Analysis of identifiable private information, even if that information was initially collected for a non-research purpose such as information obtained during a routine clinical visit;

- Use of bodily materials, such as cells, blood, urine, tissue, organs, hair, and nail clippings from living persons, even if these materials were collected by other researchers or practitioners;
- Collaborative studies in which material or information related to human subject research is collected at another institution and sent to researchers at DDEAMC; and,
- Access to medical records or data through medical information systems.

Research involving only coded private information or coded biological specimens does not constitute human subjects research if both of the following conditions are met[2]:

- The private information or specimens are pre-existing to IRB review and were not collected specifically for the currently proposed research through an interaction or intervention with living individuals; **and**
- The investigator or investigators cannot readily ascertain the identity of the subjects because:
- The key to decipher the code is destroyed before the research begins;
- The investigators and the holder of the key enter into a written agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased;
- There are IRB-approved written policies and procedures for a repository or data management center that prohibit release of the key until the individuals are deceased;
- Or there are other legal prohibitions to the release of the key.

### DDEAMC and Classified Research

DDEAMC does not participate in classified research. If the opportunity arises, guidance will be sought and policy written prior to engaging in the research.

### DDEAMC Commitment to Protecting Human Subjects

The DDEAMC HRPP is highly committed to providing ethical protections to all human subjects involved in research at DDEAMC or any of its components as noted on the Assurance documents.

### Defining "Engagement in Research"

DDEAMC, and the components covered under the DDEAMC Assurances, are engaged in human subject research in the following cases:

1. The research is conducted by or under the direction of personnel or agents of MTFs covered under DDEAMC Assurances in connection with their organizational responsibilities. "Agents" include individuals performing organizationally designated activities, or exercising

[2] Office for Human Research Protections (OHRP) Guidance on Research Involving Coded Private Information or Biological Specimens, October 16, 2008

organizationally delegated authority or responsibility (e.g., technical service contractors and visiting scientists). This includes all staff such as military, civilian and contractors.

2. The research is conducted by or under the direction of agents (military, civilian and contractors) of DDEAMC's Assurances covered MTFs using any property or facility of the organization.

3. Agents of DDEAMC's Assurances covered MTFs obtain, from any source, individually identifiable private information about human subjects for purposes of research for any purpose of the research including, but not limited to, identifying or contacting prospective human research subjects.

4. The DDEAMC's Assurances covered MTFs' agents (military, civilian and contractors) intervenes or interacts for research purposes with any human subject of the research by manipulating the environment. Examples of manipulating the environment include controlling environmental light, sound, or temperature; presenting sensory stimuli; and orchestrating environmental events or social interactions.

5. DDEAMC's Assurances covered MTFs' agents uch as military, civilian and contractors intervene or interact for research purposes with any human subject of the research by performing research procedures (this includes recruitment procedures).

An institution performing a procedure as a commercial or non-collaborative service when the named institution typically performs the service for non-research purposes (i.e., fee for service arrangements) is not engaging in the research. For example, an appropriately qualified laboratory performs routine serum chemistry analyses of blood samples for investigators solely on a commercial basis.

**Designation of the DDEAMC IRB as the IRB of Record for the DDEAMC HRPP**

All research involving human subjects or human derived materials will be reviewed by the DDEAMC IRB whenever any components covered by the DDEAMC's Assurance as described earlier in this policy are engaged in human subject research.

The DDEAMC IRB serves as the IRB of record for this HRPP. The DDEAMC IRB is a registered IRB with the DHHS OHRP and FDA under the IRB Registration Number 00003485. When DDEAMC's Assurances covered MTFs are involved in collaborative research projects with other institutions, DDEAMC may:

- Enter into joint review arrangements,
- Rely upon the review of another qualified IRB, or
- Make similar arrangements to avoid duplication of effort, in accordance with DoD regulations at 32 CFR 219.114 and DODI 3216.02, Enc 3.1.c(4).

In all cases, DoD and Army requirements must be met. Chapter 11 of the DDEAMC HRPP manual, "Collaborative Research," provides a complete discussion of these review arrangements.

### Determining if an Activity is Human Subject Research

The question of whether a planned activity is human subject research requiring DDEAMC IRB review may arise as a result of an informal inquiry to the Chief, Department of Clinical Investigations (DCI); IRB Chair; or HPA by the investigator, or at the time of submission of a protocol to the IRB. The HPA or designee will make this determination. See Chapter 6 for additional guidance.

### Ethical Foundations and Principles and Regulations Governing Human Subject Research

The ethical hallmark for human research covered by this HRPP, including protocols "exempt" under federal regulations pertaining to human subject research, are those set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* (79 Federal Register(FR) 12065, April 17, 1979). The three guiding principles of The Belmont Report are:

1. Respect for Persons: Recognition of an individual's autonomy and applied in such ways as obtaining informed consent, giving consideration to privacy and confidentiality, and adding special protections for those with diminished autonomy.

2. Beneficence: The requirement to do no harm, minimize possible harms and maximize possible benefits. Proposed research must have proper research design, competent investigators, and favorable risk/benefit assessment.

3. Justice: The principle of being fair, sharing both the burdens and benefits of research, and not exploiting vulnerable populations. The proposed research subject selection is equitable with appropriate inclusion and exclusion criteria, and does not pose an unfair burden on one group.

## 1.7 Shared Responsibilities for Protecting Human Research Subjects

The responsibility for the protection of human research subjects is a truly shared responsibility. It requires cooperation, communication, and trust among many entities. A variety of individuals contribute to the DDEAMC Human Research Protection Program (HRPP) including:

- Commander/Institutional Official (IO)
- Human Protections Administrator (HPA)
- Scientific Review Pool (SRP)
- Institutional Review Board (IRB) to include IRB Chair, IRB Vice-Chair, and IRB Members
- DCI, Chief
- RRCO Staff
- Careline/Department Chiefs
- Principal Investigators
- Other Members of the Research Team
- Research Subjects

## Commander/Institutional Official (IO)

The DDEAMC Commander is the Institutional Official (IO) for the protection of human research subjects. IAW DoDI 3216.02, Enc 2.4, the IO, under the authority, direction, and control of the Heads of the OSD and DoD Components shall:

a. Establish and maintain an HRPP to ensure the institution's compliance with this Instruction.
b. Provide the resources needed to ensure compliance with this Instruction.
c. Establish and maintain a DoD assurance and other appropriate Federal assurances, if the institution is engaged in non-exempt research involving human subjects (see Engagement section in this chapter).
d. Evaluate and improve the institution's HRPP.

The IO, in compliance with DDEAMC Assurance DoD A10015, has been granted the following authorities to ensure the highest levels of human research safety:

- To start or stop any human subject research at any component of the institution;
- To ensure that all personnel involved in human subjects research are properly educated to comply with the regulatory requirements; and
- Is positioned in sufficient proximity to be informed, engaged and committed to the human research protections program.

As DDEAMC IO, the Commander signs the DDEAMC Assurance for the Protection of Human Research Subjects and is responsible for the following:

1. Enforcing compliance with applicable federal (DoD, Army, FDA, DHHS OHRP, etc.) regulations, Command policies and guidelines, the terms of the Assurance and applicable DDEAMC policies, and procedures concerning human research activities. The IO serves as a compliance officer, approving and enforcing any IRB recommendations for the termination or suspension of a non-compliant research activity as appropriate.

2. Overseeing the establishment and maintenance of policies and procedures for the HRPP and related DDEAMC research policies and procedures.

3. Overseeing the implementation of the DDEAMC HRPP.

4. Setting the tone and providing guidance related to human subjects research.

5. Completing annual reviews of the HRPP.

6. Ensuring that the HRPP is functional and adequately staffed and funded to support (a)continuing education and training for DDEAMC IRB members and other personnel involved in HRPP functions; (b) HRPP functions such as IRB administrative review, record-keeping, and oversight of research; (c) Scientific Review; (d) IRB Review; (e) outreach to components of the Assured institution; and (f) post-approval monitoring.

7. Notifying the Clinical Investigations Regulatory Office (CIRO) and the Army Human Research Protections Office (AHRPO) of (1) any unanticipated problem involving risks to subjects or others; (2) any incident of serious or continuing noncompliance with IRB policies or regulations; and (3) any for-cause suspension or termination of IRB approval within timelines as specified in Chapter 17 Communication Plan.

**Human Protections Administrator (HPA)**

The Human Protections Administrator (HPA) position is a full-time civilian employee. The requirements of the position are extensive knowledge in conduct of research using human subjects as well as knowledge of federal and DoD regulations. The HPA helps to ensure the protection of the rights and welfare of human subjects participating in research activities; and to support the conduct of high quality and ethical human research in DDEAMC Assurance covered MTFs. The HPA is the subject matter expert and organizational contact for all internal and external human subject activities and is responsible for the following:

1. Serving as the senior advisor to the DDEAMC Commander and Chief, DCI on federal and DoD regulations related to human subjects protection.

2. The day-to-day operational and oversight responsibility for the HRPP is delegated to the HPA, who has a comprehensive knowledge of all aspects of the organization's systematic protections for human subjects.

3. Facilitating constructive communication among IO/Commander, review committee chairpersons, investigators, careline/department chiefs, and collaborative institutions as a means of maintaining a high level of awareness regarding the ethical conduct of research, and safeguarding the rights and welfare of subjects.

4. Maintaining the Organization's Assurances by providing updates in a prompt manner, arranging for ready access to DDEAMC's Assurances, copies of pertinent federal and Army regulations, policies and guidelines related to the involvement of human subjects in research, as well as DDEAMC HRPP policies and procedures.

5. The preparation and revision of policies, standard operating procedures (SOPs), and guidance documents. The HPA may designate other staff in the RRCO, or ask other DDEAMC staff to assist in the development of these documents.

6. Educating DDEAMC staff and the MTF staff covered under the Assurances to establish, promote, and maintain a culture of integrity, while also ensuring compliance with DoD and federal regulations and Institute policies relevant to the protection of human subjects.

7. Enforcing that non-exempt human subjects research may not commence until:
    a. An approved DoD Assurance covering the research exists;
    b. Ensuring that the protocol is scientifically valid as determined by the SRP
    c. The research has been approved by the IRB; and

   d. Ensuring that human subject protection records that are locally filed are maintained appropriately and are accessible only to authorized research personnel or, upon request, to authorized DoD officials.

8. Assisting the DDEAMC IRB to ensure that research conducted by the DDEAMC Assurance is conducted in accordance with all applicable regulations, policies, procedures, institutional requirements, and agreements.

9. Designating reviewers for all protocols submitted for review.

10. Ensuring prompt reporting to the DDEAMC IRB of proposed changes in a research activity, ensuring that such changes in approved research, during the period for which IRB approval has already been given, are not initiated without IRB review and approval, except when necessary to eliminate immediate hazards to the subject.

11. Ensuring the prompt reporting to the DDEAMC IRB, appropriate organizational officials, and AHRPO of any unanticipated injuries or problems involving risks to subjects or others, any serious and continuing noncompliance with the regulations or requirements of the IRB, and any suspension or termination of IRB approval for research.

12. Ensuring that appropriate oversight mechanisms to ensure compliance with the determinations of the DDEAMC IRB have been implemented.

13. Ensuring that the DDEAMC IRB reviewing research covered by DDEAMC Assurances is provided with local community and cultural factors that may affect the ethical review of protocols, both initially and for continuing review.

14. Being the HRPP contact for research subjects on all informed consent forms (ICFs).

15. Acting as the primary contact for questions pertaining to the administrative and regulatory compliance activities of the HRPP.

16. Making preliminary determinations regarding exemptions and expedited review, and providing one-on-one consultations for investigators.

17. Staying current on regulations and pending changes that affect human subject protection and advising others as appropriate.

18. Articulating all DDEAMC IRB members' duties to potential and current IRB members, and conducting an orientation for each new member appointed to the IRB.

19. Completing a robust turnover with the prospective HPA to ensure a complete and careful transition of duties and responsibilities for the protection of human subjects prior to assigning a new HPA.

20. Completing all required education requirements such as the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) Human Subject Assurance online training, Modules 1 through 3 and the Collaborative IRB Training Initiative (CITI) online training program.

**Scientific Review of Non-Exempt Human Subjects Research**

The DoDI 3216.02 states "The Department of Defense (DOD) institution shall have poliices and procedures to require scientific review of non-exempt research involving human subjects and ot ensure this review is considered during the IRB review process." The DoDI 3216.02 also requires that institutions "identify and manage conflicts of interest, not limited to financial, for DoD personnel involved in the HRPP" which is further described in Chapter 3, Conflict of Interest. The DDEAMC Scientific Review Process is charged with conducting a criteria based scientific review of non-exempt human subject research from the human research regulations that is conducted or supported by DDEAMC to include other MTF staff (military, civilian or contractor) covered under the Assurances issued by DoD and DHHS OHRP.

The DDEAMC Scientific Review Process assesses the research protocol for scientific validity and to assure that the research design will yield scientifically useful data that meet the stated objectives of the research**.** The Scientific Review Process is documented by the completion of the DDEAMC Scientific Review Process Checklist and uploading into the web-based electronic system. The scientific review will evaluate the:

A. Significance: The importance and usefulness of the study is explained. What will be the effect of this study on the concepts, methods, treatment, etc. that drives this field?

B. Feasibility: Is it feasible to conduct this study as designed? Location, time frame?

C. Purpose of the study and/or research objectives, questions, and/or hypotheses is provided.

D. Approach. Are the conceptual framework, design, methods and analyses adequately developed, well–integrated and appropriate to the aims of the study?

E. Research instruments. Are written procedures for laboratory tests such as flow cytometry, gene array, mass spectrometry, etc. available? Are copies of all written instruments such as surveys and rating scales including demographic collection forms attached?

F.Justification. Involving humans as research subjects is required as there are no alternative methodologies to adequately answer the scientific question(s). Sample size justification demonstrates that the proposed number of subjects is the minimum needed to achieve the research objectives.

G. Data collection and management plan is sufficiently described to protect the integrity of the data.

H. Data Analysis. Data analysis plan is consistent with study objectives.

I. Investigator: Is the investigator appropriately trained to conduct this study? Has the investigator brought appropriate expertise to the research team?

**Use of an External Scientific Review When DDEAMC IRB is the IRB of Record**

An external scientific review may be considered by the DDEAMC IRB during its review IAW DOD 3216.02.

**Exemption from the SR Process**

If the DDEAMC IRB is relying on a non-DOD institution, this process for SR does have to occur if the Army Human Research Protection Office (AHRPO) confirms that:

1. The collaborating non-DOD institution has an appropriate Federal assurance.
2. The involvement of DDEAMC personnel in the conduct of the research involving human subjects is secondary to that of the non-DOD institution.
3. DDAMC, the non-DOD institution, and the non-DOD institution's IRB of record have a written agreement defining the responsibilities and authorities of each organization in complying with the terms of the Federal assurances and Department of Defense Instruction 3216.02 (i.e., have an Institutional Agreement for IRB Review or similar agreement). AHRPO shall approve the terms of the agreement prior to DDEAMC's engagement in the research involving human subjects. In all cases, the IRB of a non-DoD institution reviewing non-exempt research must consider the scientific merit of the research during the IRB review.

**Scientific Review Pool Structure and Processes**

The DDEAMC relies on a procedure consisting of a scientific reviewer pool (SRP) with a SRP chairperson.

**Personnel Responsibilities and Appointments**

1. The Department of Clinical Investigation Research Regulatory Compliance Office staff provide support to the pool
2. The SRP individuals are identified by the DCI RRCO staff in consultation with the DCI Chief as well as requesting input from careline/department chiefs, the HPA and other individuals, as appropriate.
3. The SRP individuals are qualified by education and experience to evaluate the validity of the research.
4. The SRP is not restricted to a minimum or maximum number of reviewers but it must be of an appropriate size depending on the:
    a. Type of research conducted,
    b. Number of protocols reviewed annually,
    c. Expertise necessary to provide an adequate scientific review
    d. Avoidance of conflicts of interest(s)
5. All SRP individuals including the chairperson must be an experienced scientific investigator and will be appointed in writing by the Institutional Official (IO).
6. The reviewer should be technically competent, and the competence should be related to the protocol he or she is asked to review.

7. The reviewer should have the experience to understand the hypothesis of the study, the appropriateness of materials used in the study, the experimental design and methods employed by the investigators.
8. The reviewer must possess many qualities that are separate from technical expertise. The reviewer does not have to understand every facet of the study. A person may be qualified to be a reviewer because he or she understands only a part of the study.
9. The reviewer must be objective, show good judgment, be able to think logically and critically, and must be a fair and unbiased judge of the quality and significance of the work.
10. The reviewer should have no conflicts of interest and must be a good writer.
11. The number and kinds of reviewers selected to evaluate a protocol should be based on the complexity of the study itself. Investigators, the chairperson of the SRP, should weigh the technical expertise and non-technical qualities of the individuals they consider when selecting individuals to review a protocol. Also, if the HPA designates a study not greater than minimal risk, the chairperson may only select one person for the evaluation.
12. If the investigator suggests qualified individuals for the SRC, the SRP chairperson will give serious weight to the recommendations, but if the recommended reviewers do not appear to be sufficiently qualified for conducting the review, the chairperson may reject some or all of the individuals or add other qualified reviewers.

**Protocol Assignment for SR**

The DCI RRCO staff, on behalf of the SRP chairperson will assign SRP individuals to protocols based on the perceived level of risk since the determination of risk is made by the IRB and the SRP must be completed prior to IRB review:

1. The levels of risk are currently noted as:
    a. No greater than minimal risk protocols will require review by one SRP. The HPA, or designee, makes the final determination for the no greater than minimal risk protocol and only one SRP individual will be assigned.
    b. Greater than minimal risk protocols will require review by one SRP but may require additional SRP depending on the complexity of the protocol
        i. When more than one SRP individual is assigned the SR of the proposed non-exempt research, one will be name a Primary Reviewer and is responsible for serving as the lead for communication with the investigators and RRCO staff.
        ii. If the Primary Reviewer is unable to complete the SR, then another individual will be assigned.
2. The SRP individual(s) will review the submitted protocol and ancillary documents and will document their review by using the DDEAMC Scientific Review Process Checklist.
    a. When there is more than one SRP individual in the review, the Primary Reviewer is responsible for working with the reviewers either through email correspondence, or meetings to resolve any controverted issues, misunderstandings or conflicting recommendations.
    b. The Primary Reviewer is responsible for notifying the SRP chairperson and the DCI RRCO staff of the final required changes from the SRP process.
3. The SRP chairperson notifies the DCI RRCO staff to notify the investigators of the SRP decision that the protocol is:

   a. Scientifically valid as currently written and no changes are required. The research may be submitted to the IRB for review.
   b. Not scientifically valid as currently written and changes are required with re-submission to the SRP for additional review\
      i. Investigators must respond to the required changes and modify the protocol.
4. The complete results of the scientific review to include the reviewers comments are uploaded to web-based IRB system and made available to the DDEAMC IRB members for consideration during the IRB review.

All SRP individuals will conduct the review according to standard ethical principles for science reviewers (Resnik, 2011):

1. *Confidentiality*. Reviewers should maintain confidentiality throughout the review process.
2. *Respect for Intellectual Property*. Reviewer should not use the author's ideas without their permission.
3. *Professionalism*. Reviewers should read the protocol carefully, give constructive criticism, avoid personal attacks, and complete reviews on time. Reviewers should review protocols that they are qualified to review.
4. *Conflict of Interest*. Reviewers should disclose personal, professional, or financial interest that could affect the review and avoid reviewing a protocol if a conflict of interest could compromise judgment.

**Institutional Review Board (IRB)**

The DDEAMC's Institutional Review Board (IRB) has oversight over all research conducted under DDEAMC's Assurances and it serves as the central committee for the following two required oversight actions:

- Institutional Review Board
- Privacy Board for Research

The DDEAMC IRB is responsible for the following:

1. Reviewing and monitoring human research activities to ensure compliance with all applicable federal, Department of the Army (DA), MEDCOM, DDEAMC and state laws and regulations, and that the rights and welfare of research subjects are protected. The IRB is further responsible for scientific and scholarly review within the context of the risk/benefit assessment, and for conducting continuing review of approved research at intervals appropriate to the degree of risk, but not less than once per year.
2. Ensuring that independent scientific review has occurred and that this review is considered during the IRB review process.
3. Reviewing all proposed non-exempt research involving human subjects conducted under the purview of DDEAMC, determining the level of risk associated with research participation and ensuring that those risks are minimized and reasonable in relation to the procedures involved and the anticipated benefits. To this end, the DDEAMC IRB will determine which protocols will require continuing review more frequently than annually.

4. Appproving, requiring modifications to secure approval, or disapproving research.
5. Operating as a Privacy Board for research as described in the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule; 45 CFR 160 and 164) of the Health Insurance Portability and Accountability Act of 1996, and DoD 6025.18-R, DoD Health Information Privacy Regulation when research involves Protected Health Information (PHI).

**Chair, Institutional Review Board (IRB)**

The DDEAMC IRB Chair is responsible for the following:

1. Ensuring that the IRB carries out its responsibility to review each protocol for compliance with the requirements of 32 CFR 219 and, if applicable, 45 CFR Part 46, Sub Part B, C, D, and E, 21 CFR 50 and 56, 38 CFR Part 16, as well as all other applicable federal, state, DOD, and DDEAMC regulations and policies;

2. Delegating the conduct of exempt review determinations to the HPA or HPA's named and trained back-up;

3. Delegating the designation of primary reviewers for all protocols receiving expedited review and those protocols submitted for convened Committee review to the HPA or Vice Chair;

4. Sharing in primary reviews of protocols submitted for convened Committee review;

5. Reviewing reports of adverse events and unanticipated problems involving risk to subjects or others;

6. Maintaining communication with the investigators and IRB members and research administrative staff;

7. Providing oversight and leadership in conducting review of alleged cases of noncompliance;

8. Chairing the convened IRB meetings;

9. Recommending approval of the minutes of IRB meetings to the IO or AO, if appointed;

10. Reviewing policies, procedures, and forms on an ongoing basis;

11. Keeping abreast of new regulations and guidance documents involving human subjects protections;

12. Reviewing, in consultation with the Commander, HPA and Chief, DCI, the make-up and performance of the IRB;

13. Recommending IRB member appointments to the Commander;

14. Relating concerns to the command staff regarding issues in human research review;

15. Assisting in the development of IRB member training;

16. Acting as an advisor and educator to the Institution's research community and IRB members;

17. Reporting to the Commander:
    a. Any unanticipated problems involving risk to subjects or others;
    b. Any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB;
    c. Any IRB suspension or termination of IRB approval.

18. The IRB Chairperson is also the Approving Official (AO) for the use of human subjects in research. In the absence of the IRB Chairperson, the Vice-Chairperson may serve as the AO if the requisite training and education required for institutional officials and approval authorities was completed prior to the individual serving as the AO.

**IRB Vice-Chair**

The DDEAMC IRB Vice-Chair is responsible for the following:

1. Assuming the duties of the IRB Chair during the absence of the Chair;

2. Conducting expedited review of submitted protocols for initial and continuing review.

**IRB Members**

The members of the DDEAMC IRB are responsible for the following:

1. Avoiding conflict of interest in conducting reviews;

2. Completing the mandatory human protections and IRB education requirements;

3. Having an understanding of basic human research protection principles, the regulatory requirements, and IRB procedures;

4. Proposing and developing IRB policy; and

5. Maintaining confidentiality of protocols and IRB deliberations.

6. Approving only research that meets the criteria for approval under 32 CFR 219.111 and DoDI 3216.02. The members should review each protocol for the following requirements at the time of initial submission and at continuing review as noted at:

a) Title 32 CFR 219.111 and the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

ii. By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

ii. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by Title 32 CFR 219.219.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by Title 32 CFR 219.219.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. NOTE: DDEAMC does not conduct research involving prisoners.

An additional right for the IRB is to determine if observation of the informed consent process is appropriate for a specific study and if so, delegate this observation on a case-by-case basis to appropriate personnel

**HIPAA Privacy Officer**

The DDEAMC HIPAA Privacy Officer or a designated representative serves as a DDEAMC IRB member and provides subject matter expertise during convened board protocol reviews which enables the DDEAMC IRB to provide Privacy Board oversight and review for research purposes, when applicable. This individual is available as a resource to the DDEAMC IRB, HPA and investigators when guidance is sought regarding the use and disclosure of protected health information in the research setting. Each assurance covered MTF also has a HIPAA POC who is briefed during site assistance visits and each MTF is encouraged to include their local HIPAA Privacy Officer in the development of research protocols.

**Chief, Department of Clinical Investigations (DCI)**

The Chief, Department of Clinical Investigation (DCI) position is a full-time civilian employee. The requirements of the position are extensive knowledge in conduct of research using human subjects as well as knowledge of federal and DoD regulations. The DCI, Chief helps to ensure the protection of the rights and welfare of human subjects participating in research activities; and to support the conduct of high quality and ethical human research in DDEAMC Assurance covered MTFs. The responsibilities of the Chief, DCI include the following:

1. Fostering research and developing programs of human subject research for the organization.

2. Assisting the IO with enforcing compliance with applicable federal and department regulations, Command policies and guidelines, the terms of the Assurances and applicable DDEAMC policies, and procedures concerning human research activities.

3. Overseeing the establishment and maintenance of policies and procedures for the HRPP and related DDEAMC research policies and procedures.

4. Overseeing the complete implementation of the DDEAMC HRPP.

5. Conducting annual reviews of the HRPP.

6. Working with the Commander to ensure that the HRPP is functional and adequately staffed and funded to support continuing education and training for DDEAMC IRB members and other personnel involved in HRPP functions HRPP functions such as IRB administrative review, record-keeping, and oversight of research; and IRB meeting space.

7. Notifying the Commander with the HPA and DDEAMC IRB Chair for further notification to the Clinical Investigations Regulatory Office (CIRO) and the Army Human Research Protections Office (AHRPO) of any:

    a. Unanticipated problem involving risks to subjects or others;

b. Incident of serious or continuing noncompliance with IRB policies or regulations; and
c. For-cause suspension or termination of IRB approval within timelines as specified in Chapter 17 Communication Plan.

8. Serving as the DDEAMC HRPP point of contact, after the HPA, for issues dealing with the processing of individual human research protocols including levels of review, adjudication of various issues, notifications of IRB actions, progress reports or events reporting from the field to regulatory offices, etc.

9. Serving as the Project Manager for IRBNet (web-enabled software system for IRB protocol management) issues from the vendor and the Defense Medical Research Network (DMRN), the common portal for all DoD researchers for IRBNet access and other education and training materials.

10. Conducting the review for publication clearance in cooperation with the Security Officer and the Public Affairs Office (PAO).

**Department of Clinical Investigations (DCI) Research Regulatory Compliance Office (RRCO) Staff Members**

The DCI RRCO staff members are responsible for supporting and coordinating all of the activities of the HRPP and serving as the liaison between the DDEAMC IRB, IO/Commander, as well as DDEAMC and the MTFs staff covered under the Assurances, specifically in these ways:

1. Facilitating the protocol review process including an administrative review of protocol submissions;

2. Notifying investigators via IRBNet of administrative errors or deficiencies in submissions for IRB consideration;

3. Scheduling and preparing for DDEAMC IRB meetings, to include ensuring a quorum will be in attendance and arranging for conference calls if needed;

4. Drafting meeting agenda and disseminating materials for consideration by the DDEAMC IRB;

5. Communicating to investigators via IRBNet, on the behalf of the DDEAMC IRB, all committee decisions, actions, and requirements for modifications;

6. Confirming non-technical revisions to provisionally approved expedited or convened board actions prior to DDEAMC IRB approval;

7. Preparing minutes of DDEAMC IRB Committee meetings;

8. Maintaining DDEAMC IRB records, to include a complete hard copy file for protocols submitted prior to May 2009 and an electronic file for each research protocol for protocols submitted after April 2009.

9. Providing training, education, and consultation services on regulatory requirements;

10. Verifying investigators and key research personnel have completed the required human subjects protections training and notifying staff of retraining requirements;

11. Maintaining education and training records;

12. Serving as a liaison between investigators and the review committee regarding the status of their protocols;

13. Conducting administrative audits (reviews) of alleged occurrences of regulatory noncompliance in collaboration with the DDEAMC IRB;

14. Maintaining the Research Policies and Procedures site on the IKENet;

15. Maintaining a roster of DDEAMC IRB members;

16. Conducting post-approval monitoring of approved protocols as well as implementing quality assurance activities and quality improvement for the HRPP;

17. Notifying the HPA or IRB Vice-Chair of protocols or amendments received for expedited review or exempt determination.

18. Training investigators on how to use IRBNet.

19. Working with the Scientific Review Pool to ensure that non-exempt human research protocols are scientifically valid with appropriate documentation for the IRB to consider during their review and approval process.

**Careline/Department Chief**

The DDEAMC Commander/Assurance IO charges each Careline/Department Chief, as his Command Designee, with ensuring that their staff members conduct research in accordance with all applicable regulations, in a safe and ethical manner. To fulfill this charge, the Careline/Department Chief will promote a culture of respect for human subjects and for the research review process. The Careline/Department Chiefs are also responsible for nominating appropriate staff to serve on the DDEAMC IRB.

All individuals who serve as a Careline/Department Chiefs are responsible for reviewing all research activities within their service/division to ensure that:

1. Proposed research has scientific merit and has a well-organized research design;

2. Research plans are clearly presented, complete, and accurate;

3. The PI and project team have the necessary expertise and experience;

4. The proposed research is appropriate;

5. Appropriate resources are available to conduct the research; and

6. Medical or psychological resources that subjects might require as a consequence of the research are available, when applicable.

The Careline/Department Chiefs will:

- Review and sign protocol-related submissions to the IRB to affirm these conditions have been met.
- Confirm that all collaborative research efforts supported by department personnel have received appropriate approvals by the IRB and the IO/Commander.
- Review and concur with all publication clearance requests for investigators within their careline.

**Principal Investigator (PI)**

The responsibilities of the PI are addressed in Chapter 13 Investigator Responsibilities and include:

1. Acknowledging and accepting their responsibility for protecting the rights and welfare of human research subjects and for complying with all applicable provisions of the DDEAMC HRPP, including 32 CFR 219; 10 USC 980; DoDD 3216.02; where applicable 21 CFR 50, 21 CFR 56, and 45 CFR 46 (Subparts B, C, and D) under the authority of the DoD; and other federal, state and local laws, as they may relate to proposed human subjects research.

2. Ensuring that all human subject research conducted at DDEAMC, or off-site as a DDEAMC Lead Investigator, has received prospective review and approval by the DDEAMC IRB. Investigators will not make the final determination of exemption from applicable federal regulations or provisions of DDEAMC Assurances, but rather will submit requests to the DDEAMC IRB through the HPA for a determination whether the proposed research activity constitutes research or is exempt.

3. Requesting publication clearance for all written materials, including manuscripts, abstracts, and book chapters reflecting the DDEAMC or one of its covered MTFs under the Assurances. The following publications and abstracts require DDEAMC approval ***before*** the publication appears in print in a journal, book, etc.

   - Reports citing a MTF covered under DDEAMC Assurances in the title or byline;
   - Reports of DDEAMC approved research projects;
   - Reports of research performed by staff (military, civilian or contractor) assigned to an MTF covered under DDEAMC Assurances.

4. Ensuring that all subjects, or their representatives, are fully informed of the nature of the research to include potential risks to subjects.

5. Providing a copy of the DDEAMC IRB approved and signed informed consent document to each subject at the time of consent, unless the IRB has specifically waived this requirement.

6. Assuming full responsibility for subject screening and selecting subjects in strict accordance with the inclusion/exclusion criteria outlined in the application materials.

7. Implementing the research activity as it was approved by the DDEAMC IRB.

8. Ensuring that no changes in approved research are initiated without prior approval of the DDEAMC IRB, except where necessary to eliminate apparent immediate hazards to research subjects.

9. Ensuring that continuing DDEAMC IRB review and approval of the research are secured in a timely fashion and that no research continues beyond the IRB-designated approval period.

10. Reporting promptly to the DDEAMC IRB via the HPA unanticipated problems involving risks to subjects and others.

11. Selecting and ensuring that associate investigators and research personnel conduct their duties and responsibilities in fulfillment of all ethical standards and regulatory requirements for the protection of human subjects and in accordance with the terms and conditions set forth by the Assurances and the DDEAMC IRB. Maintain accountability for the actions of the research team members.

12. Maintaining complete and accurate protocol and research records (signed informed consent documents, DDEAMC IRB communications, approvals, amendments, continuing reviews, etc.) and ensuring the confidentiality and security of all information obtained from and about human subjects.

13. Ensuring designation of a new PI and orderly transfer of all protocol and research records upon reassignment, deployment, or termination.

14. Being aware of changes in protocol submission requirements.

**Other Members of the Research Team**

Every member of the research team is responsible for protecting human research subjects. These members may range from the PI, associate investigators (AI), research assistants, research coordinators, and or other research staff. Each individual member of the research team has a strict obligation to:

- Comply with all DDEAMC IRB determinations and requirements;
- Adhere rigorously to the protocol as approved; inform investigators of events or unanticipated problems involving risks to research subjects or others;
- Oversee the adequacy of the informed consent process; and

- Take whatever measures are necessary to protect the safety and welfare of research subjects.

Researchers at every level are responsible for notifying the DDEAMC IRB promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the IRB of which they become aware, whether or not they themselves are involved in the research. Researchers may also notify the DDEAMC IRB or HPA directly of any compliance concerns they may have.

**Research Subjects**

Research subjects may be viewed as having certain responsibilities as well:

- They can be expected to make every effort to comprehend the information researchers present to them so that they can make an informed decision about their participation in good faith.
- While participating, they should also make every reasonable effort to comply with protocol requirements and inform the investigators of any research-related problems.
- Subjects should notify research staff of new issues or concerns that might arise, for instance, if they are unable to meet the requirements of participation.
- Research subjects may suggest changes to the research or informed consent, where appropriate.
- Research subjects always have the right to withdraw from their participation in research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.

## 1.8 Reviews

Protection of human subjects includes an assessment of the benefits of the research and of the risks, and the determination of an appropriate and favorable ratio between the two. The scientific or scholarly merit of a research activity may affect the benefits that could result from the research and therefore impact the risk benefit equation. Research projects involving human subjects and conducted under the DDEAMC Assurances, or for which the organization is responsible, will be reviewed prior to its initiation in accordance with the guidelines or principles as discussed in this chapter.

Three levels of review are required before a research protocol, or an amendment affecting the scientific aspects of the research, is submitted to the DDEAMC IRB.

**General Review Pathway Level One – Research Team Level**

The first level of scientific review is performed at the research team level. All investigators should review the protocol for quality, relevancy, research design and statistical analysis, specific procedures, and feasibility. The research team may include collaborators who are not staff (military, civilian or contractors) of DDEAMC or the MTFs covered under the Assurances.

**General Review Pathway Level Two – Careline/Department Chief**

The second level of review is the Careline/Department Chief of the PI, who is responsible for assuring that all research protocols emanating from his or her department are relevant to the

research mission, are scientifically sound and clearly described, and that the required resources can be committed to support the research.

**General Review Pathway Level Three – DDEAMC Scientific Review Process**

The Scientific Review is considered in the deliberations of the IRB for both expedited and convened board review.

**General Review Pathway Level Four – HIPAA Privacy Board Review Process**

The HIPAA Privacy Board Review Process is implemented when the protocol uses or discloses protected health information (PHI).

**General Review Pathway Level Five – IRB Review Process**

The IRB Review Process is the last step in the review process at DDEAMC.

## 1.9 State, Territory and Local Laws

The catchment area for the DDEAMC HRPP encompasses the following states and territory:

1. Georgia
2. Alabama
3. Florida
4. Kentucky
5. Mississippi
6. South Carolina
7. Puerto Rico
8. Tennessee

The age of majority for consent in these states and territory is:

1. Georgia = Eighteen (18)
2. Alabama = Nineteen (19)
3. Florida = Eighteen (18)
4. Kentucky = Eighteen (18)
5. Mississippi = Twenty-one (21)
6. South Carolina = Eighteen (18)
7. Puerto Rico = Twenty-one (21)
8. Tennessee = Eighteen (18)

## 1.10 Protecting Human Subjects from Medical Expenses If Injured

DDEAMC will implement this requirement with guidance from AHRPO, MRMC and on a case-by-case basis IAW DoDI 3216.02:

a. DDEAMC shall establish procedures to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in DoD-conducted non-exempt research involving human subjects that involves more than minimal risk.

b. This requirement does not apply when the Department of Defense is supporting the research but is not engaged in the non-exempt research involving human subjects (i.e., when the non-exempt research involving human subjects is performed solely by non-DoD institutions).

c. DDEAMC Collaborative Research Involving Human Subjects

(1) When collaborating with a non-DoD institution, DDEAMC shall establish to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in non-exempt research involving human subjects and that are a direct result of research activities performed by DoD personnel. This does not apply to expenses resulting from the injury due to actions performed by the non-DoD institution(s).
(2) When DDEAMC personnel are conducting the research involving human subjects at the collaborating institution and the Department of Defense does not have the primary involvement, the DDEMAC is not required to have procedures to protect human subjects from medical expenses. For this purpose the determination of primary involvement shall be based on consideration of the type and portion of the DoD involvement in the collaborative research (e.g., research staff, human subjects, facilities, equipment, IRB, and all other assets).
(3) When the collaboration is such that it is difficult to separate DoD involvement from that of the non-DoD institution, the Head of the OSD or DoD Component may waive this requirement to have procedures to protect human subjects from medical expenses. AHRPO should be consulted when such a waiver is sought.

## 1.11 Annual Review of the HRPP

The HPA in coordination with the Chief and Deputy Chief, DCI; IRB Chair and Vice-Chair; and other RRCO staff will annually review the HRPP.

## 1.12 Future Goals of the HRPP

Goals for the future development of the HRPP include sychronizing the revised DoD Instruction 3216.02 with the DDEAMC HRPP and providing education and training on the revisions.

Routine monitoring of approved studies began in May 2012 and will continue to provide quality assessment and improvement activities in our compliance program. Post-approval monitoring reports will be used to determine future education and training topics as well as policy revisions or creation.

The HPA, with the Commander, worked to identify site specific point of contacts for the human research protection program for all sites in the catchment area. Due to the transitory nature of the Army, this continues to be a challenge as individuals PCS from MTF without notification to the DDEAMC Commander as we are no longer a regional asset. The RRCO will implement a semi-annual email request to the Commanders and noted research POCs to ensure that this information remains as current as possible.

## 1.13 References:

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
3. Department of Defense, Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
4. Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP) for the Protection of Human Subjects in Title 45 CFR 46 including subparts A, B, C, D, E.
5. Food and Drug Administration (FDA) Regulations for the Protection of Human Subjects in Title 21 CFR Parts 50 and 56, as applicable).
6. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in Title 45 CFR Parts 160 and 164.
7. Department of Defense Instruction 3216.02. "Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research", November 8, 2011.
8. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
9. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
10. Department of Defense Health Information Privacy Regulation, DoD 6025.18-R, January 2003
11. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.
12. Resnik, David, B. (2011). A troubled tradition: It's time to rebuild trust among authors, editors and peer reviewers, *American Scientist, 99,* 1, 2437.
13. Rockwell, Sara. (n.d.). Ethics of peer review: A guide for manuscript reviewers. Office of Research Integrity, Health and Human Services. Retrieved From htpp://ori.hhs.gov/sites/default/files/prethics.pdf

# Chapter 2: Resources Supporting the Human Research Protections Program (HRPP)

## 2.0 Purpose

The purpose of this chapter clarifies the Dwight D. Eisenhower Army Medical Center (DDEAMC) Command Group's responsibility for ensuring and providing adequate resources to support the Human Research Protection Program (HRPP) and the Institutional Review Board (IRB) functions at DDEAMC and the military treatment facilities (MTFs) covered under the two Assurances.

## 2.1 Background

Historically, the resources assigned to the HRPP did not receive a formal evaluation and as such, adjustments were not made to meet the increase in federal regulatory requirements such as the Privacy and Security requirements of the Health Insurance Portability and Accountability Act (HIPAA), increased federal scrutiny following the deaths of several research volunteers such as those reported at the University of Rochester, University of Pennsylvania and the West Los Angeles Veterans Administration and the recent Food and Drug Administration regulation requiring registration of all IRBs. Federal regulations (32 CFR 219.103(2)) and the Assurances require that DDEAMC provide adequate resources (human, technology, and funding) to support the HRPP and DDEAMC IRB.

## 2.2 Human Resources

The leadership at DDEAMC is committed to providing the required resources to support this Human Research Protection Program (HRPP). There are five key individuals responsible for oversight of the HRPP. These individuals are:

1. DDEAMC Commander/Institutional Official (IO)
2. DDEAMC Deputy Commander for Clinical Services (DCCSChief, DCI
3. Deputy Chief, DCI
4. Chair, Scientific Review
5. HIPAA Privacy Officer or designee
6. Chair, IRB; and the
7. Human Protections Administrator (HPA)
8.

The Commander/Institutional Official (IO) directs the HRPP. The DCCS supports the IO and the HRPP. The Deputy Chief, DCI, the HPA and the Research Regulatory Compliance Office (RRCO) staff support the Chief, DCI. The DDEAMC IRB Chair, in the process of carrying out the assigned responsibilities and duties, supports the HRPP. The DDEAMC IRB members, as part of the research approval process, support the IRB Chair and HPA in ensuring compliance with the HRPP requirements.

The DCI Research Regulatory Compliance Office (RRCO) consists of three FTE positions in addition to the Chief, Deputy Chief and HPA. These positions include two Research Protocol Coordinators who provide full-time administrative support and a Senior Research Compliance Specialist who conducts the audits and also serves as the electronic database administrator (for

additional information refer to Chapter 20). These key individuals, IRB members, and RRCO staff members assigned to DCI form the operational framework supporting DDEAMC's HRPP. The RRCO staff personnel under the direction of the HPA execute the day-to-day activities that are required for the DDEAMC IRB to function in compliance with the federal regulations. These activities range from the initial contact with the PI and the research team, as applicable, to the support of the convened meeting to the distribution of approval/start letters.

Over the next few years, DCI's primary goal is to reinforce and strengthen DDEAMC's focus on ensuring human protections throughout the research process. The requirements of an independent scientific review process, an active post-approval monitoring program, as well as an education and training program were listed as vital pieces that were missing from the DDEAMC HRPP by the Army Human Research Protection Office (AHRPO).

## 2.3 Space

The Chief, DCI and the RRCO staff are physically co-located at Building 38711, 7th Alley. This location is adjacent to the Telemedicine and Advance Technology Research Center (TATRC), the DCI Research and Training Laboratory (RTL), and the Dental Laboratory creating a small research hub. Future growth of the department will require additional space.

## 2.4 Fiscal Resources

The DCI is provided personnel, office and storage space, conference rooms, and information management and information technology support for the HRPP by DDEAMC. The HRPP is supported by the DCI operating budget from DDEAMC and does not include funding by any of the covered component parts or the Southern Regional Medical Command (SRMC). The DCI funds the professional training and continuing education of RRCO staff, IRB members and all investigators covered under DDEAMC's Assurances, to include:

- Courses offered by Public Responsibility in Medicine and Research (PRIM&R), and
- Online certification of human subject research training via the Collaborative IRB Training Initiative (CITI) program
-

Budgets required for the execution of individual studies are approved by DCI prior to protocol submission to the DDEAMC IRB. This review assures that studies can be executed with available funding and resources. Impact statements are obtained with the signatures from Careline/Department Chiefs impacted by a research study to verify that investigators have coordinated the support and communication required for successful study execution.

## 2.5 Matching Scientific Review and IRB Resources to Volume and Types of Human Research

### Scientific Review Workload

The research portfolio at DDEAMC consists of approximately 45 non-exempt studies which require scientific review. A pool of approximately 10 well qualified individuals with research expertise have been identified and trained to conduct criteria based scientific review before

studies are submitted to the IRB. Should turn-around time exceed five (5)-business days, additional scientific reviewers will be engaged.

**IRB Workload**

The DDEAMC IRB has one scheduled convened meeting per month. There is no anticipation that the number of IRB meetings will change drastically in the coming year.

The DDEAMC IRB workload and summary table below lists the number and type of research protocols as well as the number and type of protocol related actions reviewed by the DDEAMC IRB over the past year.

| **DDEAMC IRB Workload Summary Table**<br>*12 month period: 01 October 2011 through 15 October 2012* | | |
|---|---|---|
| 1. | Total number of active studies reviewed<br>*22 Initial Reviews and 22 Continuing Reviews, including collaborations and test plans* | 49 |
| 2. | Total number of studies reviewed and found to be exempt | 4 |
| 3. | Number of new protocols reviewed by convened committee | 6 |
| 4. | Number of new protocols approved by expedited review | 12 |
| 5. | Number of continuing review protocols reviewed by convened committee | 10 |
| 6. | Number of continuing review protocols reviewed by expedited review | 21 |
| 7. | Number of amendments requiring convened committee review | 1 |
| 8. | Number of amendments approved by expedited review | 29 |
| 9. | Number of adverse reactions/unanticipated events reviewed | 5 |
| 10. | Total number of studies reviewed and found to be non-human subject research | 9 |
| 11. | Total number of actions | 117 |
| 12. | Approximate average duration of an IRB meeting | 1 hour 17 mins |

The IRB currently has 14 members, and 8 alternate members, whose expertise provides a strong background for reviewing the ethical considerations involved in the type of research engaged in by DDEAMC. Of these members, 60% have more than one-year serving on the IRB. Expedited review is provided by 12 IRB members. At this time, 21 protocols are subject to expedited review processes, with a turn-around time that does not exceed 5-business days. Should turn-around time exceed 5-business days, additional expedited reviewers will be engaged.

## 2.6 Human Research Protection, Care of Participants, and Safety

The DDEAMC has procedures and processes, defined in this HRPP, to facilitate human research protection, care of research participants, and participant and staff safety. The DDEAMC IRB review and approval process is used to ensure that the protocol is designed to support the protection of the rights and safety of human research subjects.

For all research involving human subjects, the Careline/Department Chief of the PI will validate that the investigator has the resources and time required to execute the project. Specifically, the Careline/Department Chief will validate that the investigator will have:

- Access to a population that will allow recruitment of the required number of participants;
- Sufficient time to conduct and complete the research;
- Adequate number of qualified staff to assist with the research; and
- Adequate resources to complete the study.

Once the PI's Careline/Department Chief has validated the protocol and the resources that will be required, the protocol must be submitted to other areas affected by the study. The PI must identify all persons whose assistance will be required for the research and ensure that they are adequately informed about the protocol and their research related duties. Impactstatements must be completed by the Careline/Department Chief in each of those areas.The Careline/Department Chief include the information from the compelted Impact Statements in their operating plans and communicate this support within each department. The impact statements become part of the PI's submission package to the IRB.

**Research Monitors**

The DoDI 3216.02 establishes the requirements for a Research Monitor for all non-exempt, greater than minimal risk, research involving human subjects. A research monitor is an individual with expertise consonant with the nature of risk(s) identified within the research protocol, whose role is to protect the safety and well-being of human subjects. The DDEAMC IRB must approve an independent Research Monitor by name and provide to the Monitor, in writing their duties, authorities, and responsibilities. The duties of the Monitor shall be determined on the basis of specific risks or concerns about the research. Research Monitors have the responsibility to promptly report their observations and findings to the IRB and other designated officials. There may be more than one Research Monitor. The IRB, at its discretion, the PI, or the IO may appoint a Research Monitor for research that is not greater than minimal risk.

**Ombudsman**

The DoDI 3216.02 establishes the requirements for an Ombudsman for greater than minimal risk research involving service members as human subjects in which recruitment occurs in a group setting. An Ombudsman is a person who acts as an impartial and objective advocate for human subjects participating in research. The Ombudsman is appointed by the IRB, may not be associated in any way to the research, and must be present during the recruitment in order to monitor that the voluntary involvement or recruitment of the service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman

may, or may not, be the same person as the Research Monitor. The IRB may also appoint an ombudsman for other recruitment situations.

## 2.7 Formal Review of Resources

The formal review of resources associated with the HRPP is the initial responsibility of the Chief, DCI to evaluate workload with information provided from all members of the DCI RRCO staff. This review is shared with the IO on an *ad hoc* basis but at least twice per year.

## 2.8 Staff, IRB Leadership and IRB Member Evaluation

The work of the DCI RRCO staff will be evaluated for compliance with DoD policy and this HRPP Plan. Additional training and educational opportunities are encouraged.

The IRB members, chair, and vice chair will be evaluated by the IO. Feedback from RRCO staff, the Chief DCI, and self-evaluations will be considered in this evaluation. Additional training and educational opportunities are encouraged.

## 2.9 References:

The following references are provided for informational purposes:

1. Department of Defense Instruction 3216.02. *Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research.* November 8, 2011.
2. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
3. Army Regulation 40-7: Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances. October 19, 2009.
4. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
5. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
6. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
7. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
8. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
9. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 3: Conflict of Interest and Undue Influence

## 3.1 Purpose

The purpose of this policy is to provide guidance and education to members of the Dwight D. Eisenhower Army Medical Center (DDEAMC) human research protection program (HRPP) to identify, recognize, disclose and manage potential conflicts of interest (COI) including but not limited to financial conflicts and undue influence. This section includes researchers and team members in addition to the HRPP personnel noted below.

The DDEAMC HRPP personnel include IRB members, scientific reviewers and other individuals involved in the institutional review of research. All are required to disclose any COIs, including but not limited to financial COIs. Individuals are expressly prohibited from participating in the review of a research protocol with which they have a COI with the exception of providing information as requested by the IRB. This prohibition also extends to consultants or special expertise as requested by the DDEAMC IRB.

## 3.2 Background

Conflicts of interest (COI) may reduce the objectivity of research, or of those reviewing the research. Lack of objectivity may have an impact on the design, conduct, or reporting of research, or the analysis and interpretation of data. If research is designed or conducted improperly, its value is limited. It is not ethical to involve human subjects in research that is of no, or very limited, value. The COI may also affect subject safety. For example, a research team member with a COI may, even if unwittingly, bias the consent discussion by minimizing the risks or overstating the benefits. Conflicting interests may also affect a research team member's willingness to report adverse reactions possibly related to the research intervention. Research team members with a COI may also improperly include or exclude subjects.

Undue influence may exist when someone attempts to influence a DDEAMC IRB member or junior study team member. For example, in the military setting, a junior ranking personnel may be assigned to review or execute the research study of a more senior officer. Junior personnel may be vulnerable to excessive pressure (undue influence) in carrying out their study related responsibilities. This undue influence must be identified and managed.

## 3.3 Definitions

**Conflict of Interest** – A set of conditions in which a reasonable person could perceive that an investigator's judgment concerning a primary interest (e.g., subject welfare, integrity of research) could be biased by a secondary interest (personal or financial gain). IAW DoDI 3216.02, November 8, 2011, this definition applies to anyone or their immediate family member's involved in the HRPP process, not just the investigators or IRB members.

**Financial Conflicts of Interest -** A COI is a significant financial interest that would reasonably appear to affect or, to be affected, by the research. A COI most often arises from an individuals' financial relationship with a "sponsor" of the research.

**Individual Conflict of Interest** – An individual's or an individual's immediate family member's (defined as spouse, children, siblings, parents, equivalents by marriage [in-laws], or other household members) financial or time arrangements with an organization that sponsors research or is otherwise a benefactor of the institution and may create, or appear to create, a competing interest for the individual. IAW DoDI 3216.02, November 8, 2011, this definition applies to anyone or their immediate family member's involved in the HRPP process, not just the investigators or IRB members.

**Institutional Conflict of Interest –** Situations in which the institution, members of senior leadership or affiliated organizations have an interest in the research which may create an environment of undue influence in the implementation and conduct of the research.

**Recuse -** The IRB members leave the room during the final discussion and vote on any protocol action where they may have a conflict of interest.

**Significant Financial Interest -** A significant financial interest means anything of monetary value, including but not limited to the following:

a. Receiving or expecting to receive compensation in which the value of compensation could be affected by the outcome of the study.

b. A proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright, royalties, or licensing agreement.

c. Any equity interest in a publicly held company that exceeds $10,000 in value or represents more than a five percent (5%) ownership. The requirement applies to interests held during the time the research team member is carrying out the study and for one (1) year following completion of the study.

d. Any equity interest in the sponsor of a covered study (i.e., any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices.) This requirement applies to all covered studies, whether ongoing or completed.

e. Significant payments of other sorts, which are payments that have a cumulative monetary value of $25,000 or more made by the sponsor of a covered study to the research team member or the research team members' Institution, to support activities of the research team member exclusive of the costs of conducting the clinical study or other clinical studies (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical research team member is carrying out the study and for one (1) year following completion of the study.

The term does **NOT** include the following:

a. Salary, royalties, or other payments from the institution conducting the research or from the U.S. Army or any organizational unit within the Army;

b. Ownership interests in the institution conducting the research;

c. Salary, royalties, or other payments that are not expected to exceed $10,000 over the next twelve (12) months.

The financial interests of a research team member include the financial interests of the research team member's spouse and dependent children.

**Sponsor -** A sponsor is any organization, institution, company, or other entity financially supporting a study.

### 3.4 Guidelines for Research Team Members

All research team members (including principal investigators, associate investigators and study coordinators) must identify and self-disclose any COI including but not limited to significant financial interest with a research sponsor, and any other significant financial interest that may reasonably appear to affect, or be affected by, their research upon the submission of new protocols. This action is accomplished by the completion and submission of the Conflict of Interest Disclosure Form in the web-enable software system to the DDEAMC IRB. The COI disclosure must be updated if the research team member acquires new significant financial interest with a sponsor, or new significant financial interests that may otherwise reasonably appear to affect or be affected by the research, during the conduct of research, the data analysis, or the reporting of results of the research. Additionally, research team members are required to update their disclosure at the time of their research protocol's continuing review. The COI disclosure must be included within the protocol package. Disclosure will include the following:

1. The name of the research team member, title, and organization, the title of the research protocol, and identification of the COI;
2. A list of all significant financial interests with a research sponsor, and all other significant financial interests that may reasonably appear to affect or be affected by the research. The list must include the name of the organization in which the research team member has an interest, the nature of the interest (e.g., salary, equity, intellectual property rights), and a detailed description of the interest including the approximate dollar amount.

### 3.5 Determining the Existence and Nature of a Conflict of Interest

The DDEAMC IRB is tasked to evaluate whether the research involves financial relationships or other COI that may potentially harm a research subject or compromise the integrity of the research, and to determine what actions are necessary to protect human subjects and to ensure those actions are taken. The DDEAMC IRB, organization, and the research team members will consider the following factors when determining the existence and nature of a conflict of interest:

1. How is the research supported or financed?
2. Where and by whom was the study designed?
3. Where and by whom will the safety and efficacy data be analyzed?
4. What are the financial relationships between the research team members and the sponsor?
5. Does the research team member have any proprietary interests in the product including patents, trademarks, copyrights, and licensing agreements?
6. Does the research team member have equity interest in the sponsor?
7. Does the research team member or DDEAMC or any of the MTFs covered by the

Assurances receive any compensation that may be affected by the study outcome?

8. Does the research team member or DDEAMC or any of the MTFs covered by the Assurances receive payment of other sorts? (I.e., grants, compensation in form of equipment, retainers for outgoing consultation, and honoraria.) If so, what are the arrangements for payment? Does the payment go to the institution or the research team member?
9. What is the payment per participant or incentive payments, and are those payments within the norm?
10. Given the financial relationships involved, is DDEAMC or any of the MTFs covered by the Assurances the appropriate site(s) for the research?
11. Are there mechanisms in place to separate responsibilities for financial decisions and research decisions?

### 3.6 Management of Research Team Member Conflicts

If the DDEAMC IRB determines that any of the disclosed interests are in conflict, the IRB will determine how to satisfactorily resolve the conflict of interest.

1. Conflicts should be eliminated, if possible. Examples of possible actions to eliminate a COI include, but are not limited to, divestiture of the interest, severance of the relationship that creates the interest, or disqualification of the research team member from participating in the research.
2. If a research team member cannot eliminate a COI, the research team member must manage or reduce the scope of the conflict. Examples of possible actions to manage or reduce conflicting interests include but are not limited to these:
    a. Modifications to the research plan;
    b. Monitoring of the research or consent process by independent reviewers;
    c. Having a non-biased third party obtain consent, especially when potential conflicts could influence the tone or presentation of information during the consent process.
3. If the DDEAMC IRB believes that a conflicting interest cannot be eliminated, and that the conflict could be considered material to a potential subject's decision-making process (i.e., when a subject is assessing the risks and benefits or the merits of the research itself), the research team member must inform the subject in the consent process and consent form of the existence and nature of the conflict of interest. The consent process and form should also document how the COI is being managed, and what additional protections have been put in place.
4. Subject must be informed in easily understandable language.
5. Research team members should disclose to subjects only conflicts of interest, not other financial interests.
6. The dollar amount of the financial interest should not be disclosed to the subject.

The DDEAMC IRB will not approve research until it is satisfied that significant COI have been

eliminated, managed, or reduced.

### 3.7 Eliminating or Mitigating a Conflict of Interest

Given the presence of a significant COI, the DDEAMC IRB will determine if the rights and welfare of the human subjects would be better protected by any or a combination of the following:

- Elimination or reduction of the COI.
- Disclosure of the COI to the prospective subjects.
- Separation of responsibilities for financial and research decisions.
- Additional oversight or monitoring of the research.
- An independent data and safety monitoring committee (DSMC).
- Modification of roles of particular staff (i.e., a change of the person who seeks consent, or a change of the research team member)

The DDEAMC IRB will not approve research until it is satisfied that significant COI have been:

- Eliminated
- Managed or
- Reduced

### 3.8 Disclosure to Subject in Consent Process

For approved research in which significant COI cannot be eliminated, the DDEAMC IRB may require disclosure of the specific COI in the informed consent process and form. The consent process and form will include how the COI is being managed and what protections have been put in place.

### 3.9 Failure to Comply with the Conflict of Interest Policy

The DDEAMC IRB may suspend research if they believe that an existing COI is deemed to threaten subject safety or integrity of the research, or upon discovery that an undisclosed significant COI exists.

### 3.10 Guidelines for DDEAMC HRPP Members

#### IRB Members

No member of the DDEAMC IRB may participate in the initial or continuing review of any project in which the member has an actual or perceived conflicting interest, except to provide information at the IRB's request. The COI of an IRB member includes significant financial conflicts of interest as defined above, as well as the following:

- Participation in the project either as an research team member or a member of the research team;
- Supervision of the project or the research team member;
- Personal relationship with, or related to, the research team member;
- Fiduciary relationship to the sponsor (e.g., IRB member serves on the company's board of directors);

- Personal or professional adversarial relationship with the research team members.

An IRB member that was recused from the voting process may not be counted as part of the quorum for that protocol action. The DDEAMC IRB may not vote on any actions related to the protocol should the quorum fail. In this case the protocol will be placed on the agenda of a future convened meeting.

**Scientific Reviewers**

Individuals who act as scientific reviewers may not participate in the initial or continuing review of any project in which the member has an actual or perceived conflicting interest, except to provide information at the HRPP's request. The COI of an scientific reviewer includes significant financial conflicts of interest as defined above, as well as the following:

- Participation in the project either as an research team member or a member of the research team;
- Supervision of the project or the research team member;
- Personal relationship with, or related to, the research team member;
- Fiduciary relationship to the sponsor (e.g., scientific reviewers serves on the company's board of directors);
- Personal or professional adversarial relationship with the research team members.

**DCI Staff including RRCO**

No member of the DCI staff may participate in the review of any project in which the staff member has an actual or perceived conflicting interest, except to provide information at the HRPP's request. The COI of a DCI staff member includes significant financial conflicts of interest as defined above, as well as the following:

- Participation in the project either as an research team member or a member of the research team;
- Supervision of the project or the research team member;
- Personal relationship with, or related to, the research team member;
- Fiduciary relationship to the sponsor (e.g., DCI staff member serves on the company's board of directors);
- Personal or professional adversarial relationship with the research team members.

## 3.11 Consultants or Special Expertise

Consultants or special expertise as requested by the DDEAMC IRB are prohibited from participating in the review of a research protocol in which they have a COI, except to provide information as requested by the DDEAMC IRB. Consultants, like other stakeholders in the HRPP, will be asked to self-identify and disclose any potential financial COI at the time of review assignment.

Consultants will be asked to recuse themselves from the room prior to the final DDEAMC IRB discussion and voting. Consultants are not considered as part of the quorum.

## 3.12 Undue Influence and Coercion

Undue influence is usually described as the exertion of pressure to limit the amount of free will that an individual has to make a decision. Coercion is generally defined as the use of physical or psychological force or threats of such force.

### Research Subjects and Undue Influence or Coercion

Unit officers and non-commissioned officers (NCOs) are specifically restricted from unduly influencing the decisions of their subordinates to participate or not participate as research subjects. Unit officers and senior NCOs in the chain of command are required to be absent during research subject solicitation and consenting activities.

Professional ethics and regulatory requirements (32 CFR 219.116 prohibit the coercion of human subjects to take part in research efforts or to remain in a study against their will. In the informed consent process, and in all other processes, all research team members will ensure that this mandate is strictly enforced.

The consent briefing and the informed consent form may not make claims of effectiveness or overstate the possible benefits of the research. The consent form should not include the phrase "I understand" and should not require participants to certify completeness of disclosure.

The Army's research and development mission should not override or obscure review and approval procedures. The DDEAMC's IRB may consider an urgent or compelling need for the research in determining the military relevancy and benefits of an activity, but may not short-circuit a thorough analysis of the protocol.

### HRPP Members and Undue Influence Or Coercion

The DDEAMC Institutional Official (IO) will investigate and resolve any reported attempt to inappropriately pressure a review committee chair or DCI staff member to secure a particular determination or outcome.

Any attempt to exercise undue influence or coercion over the DDEAMC IRB or any other Human Research Protection Program (HRPP) unit should be reported as follows:

1. A DCI staff member who experiences undue influence should first report the occurrence to the DCI Chief or DDEAMC IRB Chair, who will attempt to mediate or resolve the concern, in consultation with the appropriate Department Chief, Deputy Commander, or Commander, as necessary or appropriate.
2. A DDEAMC IRB member who experiences undue influence should first report the occurrence to the IRB Chair, who should notify the Chief, DCI. Together they will attempt to mediate or resolve the concern, in consultation with the Deputy Commander, or Commander, as necessary or appropriate.
3. If the IRB Chair experiences undue influence, he/she should first report the occurrence to Chief DCI. The Chief, DCI will attempt to mediate or resolve the concern, in consultation with the appropriate Deputy Commander or the Commander, as necessary or appropriate.

## 3.13 References:

The following references are provided for informational purposes:

1. Department of Defense Instruction 3216.02. *Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*. November 8, 2011.
2. Title 21 CFR 54, Financial Disclosure by Clinical Research team members 21 CFR §54.2(a)-(d), 21 CFR §54.2(f), 21 CFR §54.4(a)(3), 21 CFR §54.4(b)
3. Food and Drug Administration (FDA) Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
4. Title 42 CFR 50, Subpart 4, Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought 42 CFR §50, 45 CFR §690
5. Draft Guidance Document, DHHS, Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection, March 31, 2003
6. Title 32 CFR 219, Protection of Human Subjects
7. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 4: Education and Training on Human Research Protections

## 4.1 Purpose

The purpose of this policy is to describe the initial and continuing education and training on human research protections at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 4.2 Background

The DoD Instruction 3216.02, "*Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*," as well as the Memorandum for Surgeon General, US Army, Minimum Education Requirements for DoD Personnel Involved in Human Research Protection, dated 16 August 2012 requires that all DoD personnel involved in the conduct, review, or approval of research involving human subjects, including the non-affiliated and prisoner representative members on the DoD IRB, receive initial and continuing education and training.

a. Initial and continuing education and training shall be commensurate with the duties and responsibilities of the DoD personnel.
b. All training and education of DoD personnel shall be documented.
c. Professional certification in the field of human research protection is encouraged for all DoD personnel involved in review and oversight of research involving human subjects.
d. When assessing whether to support or collaborate with a non-DoD institution for research involving human subjects, the DoD Components should evaluate the non-DoD institution's education and training policies to ensure the personnel are qualified to perform the research. The rigor of the evaluation should be appropriate for the complexity and risk of the research.

## 4.3 Policy

As part of DDEAMC's Department of Clinical Investigations (DCI) Research Regulatory Compliance Office (RRCO) performance improvement efforts, the department is in the process of building a stronger research and human subjects protection education and training program using the Assistant Secretary of Defense for Research & Engineering ((ASD(R&E)) Minimum Education Requirements for DoD Personnel Involved in Human Research Protections. Training requirements are based upon roles and associated responsibilities. HRPP roles and associated minimum training requirements are presented in the following areas:

**Section 4.4.1 HRPP Role Categories and Meeting of Training Requirements**
Identifies whom and how the requirements can be met;
**Section 4.4.2 Table: Role Based Education and Training Topics**
Identifies role related training topics; and
**Section 4.4.3 Explanation of Educational Topics**
Identifies content of the training topics.

When personnel participate in more than one HRPP role, the person is required to meet the training requirements for each role (example, an investigator is also an IRB member). Personnel must complete their required training before assuming their HRPP duties. All personnel must complete in the required educational topics in human research protections every three years. They must also participate in continuing education during the intervening years.

DDEAMC generally accepts the completion of the Collaborative Institutional Training Initiative (CITI) biomedical or social-behavioral program as meeting the minimum training requirements for investigators, however, additional training may be required based upon the investigators area of research. Example: An investigator conducting a clinical investigation regulated by FDA must also complete GCP training.

The Institutional Official (IO), Chief and Deputy Chief DCI, HPA, and Institutional Review Board (IRB) Chair must also complete assurance training. The educational briefs developed at the Department of Health and Human Services (DHHS) Office of Human Research Protection (OHRP) for Assurance Officials will be used for this purpose. The IO will complete at least module 1 and the other four will complete all three modules of this training. The OHRP Assurance Training is found at http://ohrped.od.nih.gov/CBTs/Assurance/login.asp.

The IOs must also receive DoD assurance training provided by AHRPO before assuming the IO responsibilities.

Exempt Determination Officials must be trained directly be AHRPO before making “not human subject research” and “exempt” determinations.

New IRB members are required to review the DDEAMC HRPP Plan and complete required CITI training within thirty (30) days of their New Member Orientation session. The DDEAMC IRB members will also review the Department of Health and Human Services (DHHS) OHRP “Protecting Human Subjects” three (3) instructional modules. All DDEAMC IRB members are required to take a minimum of four hours of research ethics and/or human research protections training continuing education each year. The HPA and IRB Chair are responsible for developing a continuing education program for IRB Committee members, and for documenting completion of such training by IRB members. The DDEAMC IRB members will also periodically receive a list of references and educational materials that can be accessed through the DDEAMC Intranet.

The PI is responsible for ensuring, and documenting in the protocol file, that all individuals involved in the design and conduct of a study have met the training requirements of this policy.

- Individuals who collaborate with DDEAMC in human subject research are expected to meet the training requirements of their parent institution. However, if collaborating personnel are from an institution without a human subject protections training requirement, they must complete the DDEAMC-required training appropriate to their role in the research and

provide documentation of that training to the DDEAMC HPA or lead investigator for placement in the protocol file.

Reference materials, including all relevant Department of the Army (DA) Research Regulations, are maintained in the DCI RRCO.

## 4.4 HRPP Roles and Training Requirements

### 4.4.1 HRPP Role Categories and Meeting of Training Requirements

Common roles in the DoD HRPPs have been grouped into 10 categories, with each category assigned required training. Each category is described below (1 – 10). Personnel who cannot identify their role(s) within the HRPP should contact the HPA for guidance.

***Category 1. Institutional Officials (IO):*** The senior person authorized to establish and responsible to maintain the HRPP for the DoD institution. If the institution has a Federal assurance, this is the individual in the institution who signs the Federal assurance and is responsible for the institution's compliance with the terms of the assurance.

Meeting Initial Training Requirement

- OHRP Assurance Training http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp
- DoD assurance training provided by AHRPO.
-

Continuing Education

- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly
- CITI Basic Course for IRB Members
- CITI Refresher Course for IRB Members

***Category 2. Not applicable to DDEAMC***

***Category 3. Institutional Review Board Members:*** All members of the IRB (e.g., Chairs, co-Chairs, primary members, alternate members, prisoner representative, community members, etc.). Consultants (i.e., non-voting members) to the IRB are not required to have the same level of education as the voting members, but at a minimum should be educated on the ethics, policies, or other topics for which they are being asked to consult.

Meeting Initial Training Requirement

- CITI Basic Course for IRB Members
- Exempt Determination Official Training by AHRPO (for EDO only)
- Read DDEAMC HRPP Plan
- Complete New Member Orientation
- Review Department of Health and Human Services (DHHS) OHRP "Protecting Human Subjects" three (3) instructional modules.

Continuing Education

- CITI Refresher Course for IRB Members
- Training at IRB Meetings
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly
- DoD assurance training provided by AHRPO (IRB Chair) Chief and Deputy Chief DCI, and HPA

***Institutional Review Board Support Staff****:* The personnel supporting the IRB members (e.g., staff who are advising the investigators, conducting preliminary review of protocols before submission to the board, and providing training to HRPP personnel).

Meeting Initial Training Requirement

- CITI Basic Course for IRB Members
- Read DDEAMC HRPP Plan
- Exempt Determination Official Training by AHRPO (for EDO only)

Continuing Education

- CITI Refresher Course for IRB Members
- Training at IRB Meetings
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly
- DoD assurance training provided by AHRPO (Chief and Deputy Chief DCI, and HPA)

***Category 4. Advisors to the Institutional Official*****:** Personnel (e.g., attorneys, ethicists) outside of the IRB and IRB Office who provide an interpretation of part 219 of title 32, Code of Federal Regulations (32 CFR 219), DoDI 3216.02, and other HRPP policies to the institutional official.

Meeting Initial Training Requirement

- CITI Basic Course for IRB Members

Continuing Education

- CITI Refresher Course for IRB Members
- DoD assurance training provided by AHRPO
- Additional CITI modules
- Individual Training
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly

***Category 5. Investigators*****:** Personnel who are responsible for creating the research protocol and/or conducting the research. There may be more than one investigator on a protocol.

Meeting Initial Training Requirement

- CITI Basic Course for Investigators, Team Members

Continuing Education

- CITI Refresher Course for Investigators, Team Members
- Additional CITI modules
- Individual Training
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly

***Category 6. Research Support Personnel***: Personnel who are engaged in the research, but who are participating in a limited and/or defined part of the research protocol under the direct supervision or guidance of an investigator.

Meeting Initial Training Requirement

- CITI Basic Course for Investigators, Team Members

Continuing Education

- CITI Refresher Course for Investigators, Team Members
- Additional CITI modules
- Individual Training
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly

***Category 7. Research Monitors, Ombudsman, Subject Advocates, Data Safety Monitoring Boards (DSMBs)*:** Personnel who are not part of the research team and who have been appointed by the IRB or are identified in the IRB-approved protocol to act on behalf of the IRB (e.g., Research Monitor or Ombudsman) or on behalf of the research subject (e.g., Subject Advocate). Personnel in this category should be educated on the ethical and regulatory topics at a depth appropriate for which they are being tasked.

Meeting Initial Training Requirement

- CITI Basic Course for IRB Members

Continuing Education

- CITI Refresher Course for IRB Members
- Additional CITI modules
- Individual Training
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly

***Category 8. Research Coordinators, Clinical Coordinators, Study Coordinators, and Research***

***Administrators*:** Personnel, such as the Research Coordinators, Clinical Coordinators, Study Coordinators, and Research Administrators, responsible for conducting the research under the auspices of the investigator(s) or personnel involved in the preparation and administration of research protocols.

Meeting Initial Training Requirement

- CITI Basic Course for Investigators, Team Members

Continuing Education

- CITI Refresher Course for Investigators, Team Members
- Additional CITI modules
- Individual Training
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly

***Category 9. Regulatory Oversight of Extramural Human Subject Research*:** Personnel involved in ensuring the research involving human subjects that is supported by DoD, but conducted by non-DoD institutions, is compliant with DoD Component policies. For extramural contracts, this role is known as the Human Research Protection Official (HRPO).

Meeting Initial Training Requirement

- CITI Basic Course for IRB Members

Continuing Education

- CITI Refresher Course for IRB Members
- Additional CITI modules
- Individual Training
- Attendance at PRIM&R
- Participation in CIP DCO Series – bi-weekly

***Category 10. Research Subjects*:** Personnel participating in human subject research.

- CITI modules

## 4.4.2Table: Role Based Education and Training Topics

| Educational Topics | | HRPP Role Category # | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| R = Required<br><br>A=Required when applicable to the person's scope of research or management responsibilities<br><br>O=Optional; Person is encouraged to take topics | | 1 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| A | Ethical Principles of & Requirements for an HRPP | R | R | R | R | R | R | R | R | O |
| B | Defining Human Subject Research and Applying the Exemptions | R | R | R | R | R | R | R | R | O |
| C | Identifying and Mitigating Subject Risk and Subject Selection | O | R | A | R | O | A | R | R | O |
| D | Research with Pregnant Women, Human Fetuses, and Neonates | O | A | A | A | A | A | A | A | O |
| E | Research with Prisoners | A | A | A | A | A | A | A | A | O |
| F | Research with Children | A | A | A | A | A | A | A | A | O |
| G | Research in an Educational Setting or with Students | O | A | A | A | A | A | A | A | O |
| H | Use of a Research Monitor | A | R | A | R | R | R | R | R | O |
| I | Informed Consent | O | R | A | R | R | R | R | R | O |
| J | 10 USC 980 | A | R | A | A | O | A | O | R | O |
| K | Privacy and Confidentiality | A | R | A | R | R | R | R | R | O |
| L | Identifying and Mitigating Conflicts of Interest | R | R | R | R | R | R | R | R | O |
| M | Requirements for IRB Review and Approval | O | R | A | R | O | A | A | R | O |
| N | IRB Operating Requirements | A | R | A | O | O | O | A | R | O |
| O | Research with the Department of Veteran's Affairs | O | A | A | A | A | A | A | A | O |
| P | International Research | O | A | A | A | A | A | A | A | O |
| Q | Internet Research | O | A | A | A | A | A | A | A | O |
| R | Records-Based Research | O | A | A | A | A | A | A | A | O |
| S | Genetics Research | O | A | A | A | A | A | A | A | O |
| T | FDA Regulated Research | O | A | A | A | A | A | A | A | O |
| U | HIPAA Regulated Research | O | A | A | A | A | A | A | A | O |

### 4.4.3 Explanation of Educational Topics

***Educational Topic A.*** Ethical Principles of and Requirements for a HRPP

- The Belmont Report
- 32 CFR 219
- DoDI 3216.02
- DoD Component Policies (each DoD Component will identify their unique policies and procedures)

***Educational Topic B.*** Defining Human Subject Research and Applying the Exemptions

- The definition of research (as used in 32 CFR 219 and DoDI 3216.02)
- The definition of human subject (as used in 32 CFR 219 and DoDI 3216.02)
- When human subject research can be exempt from requiring the institution to have a Federal assurance and requiring an IRB review of the research (as described in 32 CFR 219 and DoDI 3216.02)
- Limitations for applying the exempt categories to pregnant women, fetuses, neonates, children, and prisoners (as described in 32 CFR 219 and DoDI 3216.02)

***Educational Topic C.*** Identifying and Mitigating Subject Risk and Subject Selection

- Implications of Section 6 of Enclosure 3 of DoDI 3216.02
- Probability and magnitude of harm
- Assessing the subject population
- Assessing risk from the subject's perspective
- Balancing risks and potential benefits
- Minimizing and managing risk
- When documentation of informed consent imposes risk
- Equitable subject selection and implications of section 252 of Public Law 103-160

***Educational Topic D.*** Research with Pregnant Women, Human Fetuses, and Neonates

- Implications of Section 7 of Enclosure 3 of DoDI 3216.02
- When to exclude women of childbearing years versus pregnant women

- Appropriate informed consent language

***Educational Topic E.*** Research with Prisoners

- Implications of Section 7 of Enclosure 3 of DoDI 3216.02
- Special composition of the IRB
- Requirements for additional IRB considerations and DoD approvals

***Educational Topic F.*** Research with Children

- Implications of Section 7 of Enclosure 3 of DoDI 3216.02
- Definitions of "risk" and "minor increase in risk"
- Legal requirements for consent and assent
- Developing assent agreements and obtaining assent for various ages of children

***Educational Topic G.*** Research in an Educational Setting or with Students

- Implications of Sections 7 and 12 of Enclosure 3 of DoDI 3216.02
- Definitions of "risk" and "minor increase in risk"
- Legal requirements for parental consent and child assent
- Identification and mitigation of vulnerabilities of students
- Common DoD and Federal requirements for conducting research in school systems

***Educational Topic H.*** Use of a Research Monitor

- DoDI 3216.02 requirements for the research monitor
- Process to waive the requirement for a research monitor

***Educational Topic I.*** Informed Consent

- Requirements for the overall informed consent process
- Requirement for disclosing DoD support of the research and access to subject data
- Requirements for the informed consent document
- Requirements for waiver of informed consent
- Requirements for waiver of documentation of informed consent
- Requirements for investigator changes to the informed consent process

***Educational Topic J.*** 10 US Code (USC) 980

- 10 USC 980 requirements for informed consent
- Definition of research involving an experimental subject
- Process to waive requirement for informed consent

***Educational Topic K.*** Privacy and Confidentiality

- Definition of and maintaining the privacy of research subjects
- Determining what is public and private data
- Definition of and ensuring confidentiality of research data
- Limitations of "promising" subjects confidentiality of subjects' data
- Federal and state reporting requirements

***Educational Topic L.*** Identifying and Mitigating Conflicts of Interest

- Identifying types of conflicts of interest impacting research involving human subjects
- Tools to mitigate such conflict of interest
- What and when to disclose to the institution, the IRB, and/or the subjects

***Educational Topic M.*** Requirements for IRB Review and Approval

- 32 CFR 219 requirements relevant to criteria for IRB approval of research protocol (including the informed consent process)
- DoDI 3216.02 requirements for DoD Component administrative review
- Requirement for minimizing the number of IRB and oversight reviews
- Requirements for expedited review
- Requirements for continuing review
- Requirements to review changes to the protocol or informed consent process
- Requirements for deception research

***Educational Topic N.*** IRB Operating Requirements

- Requirements, role, authority, and composition of the IRB
- IRB requirements for approving research
- Requirements for expedited and IRB review

- Policies and procedures for reporting and communicating with the investigator, Institutional Official, and DoD Component Headquarters Office

***Educational Topic O.*** Research with the Department of Veteran's Affairs (VA)

- Unique aspects about the VA patient population
- Key applicable VA human subjects protections requirements
- Procedures for conducting research with the VA Medical Centers
- VA office overseeing research involving human subjects
- VA accreditation program
- VA-specific requirements for protection of human subjects
- IRB Requirements

***Educational Topic P.*** International Research

- International and country-specific ethical standards and regulations
- Relationship between United States and DoD requirements and foreign cultures
- U.S. Government guidelines
- Applicable FDA regulations
- Host-nation approval and nations without an approval process
- Local IRBs and obtaining local input to IRB review
- Cultural sensitivity
- Requirement for disclosing DoD support of the research and access to subject data

***Educational Topic Q.*** Internet Research

- Requirements for consent
- Identifying and mitigating privacy issues
- Assessing risk (including the ability to identify)
- Information Technology issues when using the DoD computer or internet

***Educational Topic R.*** Records-Based Research

- Identifying and mitigating privacy and confidentiality risk
- Applying the exempt criteria
- Requirement for convened IRB committee review or expedited review
- Requirements for informed consent or waiver of informed consent

***Educational Topic S.*** Genetics Research

- Identifying, mitigating, and communicating to the subject the risks of harm
- Assessing risk regarding privacy and confidentiality
- Considerations of family members
- Obtaining informed consent
- Using stored samples
- Future use of samples
- Obtaining familial medical history from the subject

***Educational Topic T.*** FDA Regulated Research

- FDA regulations
- Differences between 32 CFR 219 and the FDA regulations
- FDA requirements for emergency use, emergency medicine research, and applicability of 10 USC 980
- FDA required training (e.g., Good Clinical Practices (GCP))

***Educational Topic U.*** Health Insurance Portability and Accountability Act (HIPAA) Regulated Research

- Who is a covered entity
- What is protected health information (PHI)
- Requirements for an authorization for disclosures of PHI
- Requirements for a waiver of an authorization for disclosures of PHI

## 4.5 Collaborative IRB Training Initiative (CITI) Website Training Requirement

Federal regulations for human use research require extensive training for HRPP personnel. The website address is www.citiprogram.org.

CITI Completion certificate will be issued by CITI after successful completion of the course. The certificate must be submitted in the User Profile of the electronic web based IRB submission system. Delays in completing the required training will result in a delay of review or approval release of the protocol by the DDEAMC IRB.

## 4.6 Acceptance of Other Education Programs

The DDEAMC IRB will accept training offered by other providers, although additional documentation may be required to verify program content.

## 4.7 Other Educational Opportunities

There are several opportunities for education to include the following:

- *Clinical Investigation Regulatory Office (CIRO), Clinical Investigation Program (CIP) Education Program* - Offered via DCO on a bi-weekly basis to all members of the HRPP
- i is offered by DCI nursing staff
- *Research Consults* – Offered by DCI staff as needed in the DDEAMC facility for individual training and consultation on developing or continuing research projects
- An *initial DCI Orientation* is offered annually for all new participants in the graduate medical and dental education programs.
- Monthly *IRBNet training* is offered by DCI staff on the second Wednesday of each month in the DDEAMC facility.
- *Resident Briefings* – as requested by departments
- IRB members receive training as most monthly IRB meetings

Individual training is encouraged and is available upon request.

## 4.8 References

The following references are provided for informational purposes:

1. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. December 28, 2001.
2. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2000.
3. Department of Defense Instruction 3216.02, "*Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*," November 8, 2011
4. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
5. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.

6. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
7. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
8. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
9. DoD Health Information Privacy Regulation, DoD 6025.18-R, January 2003
10. *Responsible Research: A Systems Approach to Protecting Research Subjects,* Institute of Medicine, 2003.
11. *The Belmont Report*: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research,* 1979. Office Of The Assistant Secretary Of Defense, Research and Engineering, SUBJECT: Minimum Education Requirements for DoD Personnel Involved in Human Research Protection, dated 16 August 2012
12. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.
13. Assistant Secretary of Defense for Research & Engineering ((ASD(R&E)) Minimum Education Requirements for DoD Personnel Involved in Human Research Protections, August 2012

# Chapter 5: FDA Regulated Research

## 5.1 Purpose

The purpose of this policy is to outline the responsibilities and provide guidance about Food and Drug Administration (FDA) regulated clinical investigations involving test articles that are conducted by or at the Dwight D. Eisenhower Army Medical Center (DDEAMC) and the institutions under its covered Assurances.

## 5.2 Background

The use of an FDA-regulated test article in clinical investigations involving human subjects requires prospective convened DDEAMC IRB approval prior to its use at DDEAMC. The Human Protections Administrator in consultation with the IRB Chairperson and/or USAMMDA reviews the documents provided by the sponsor to determine if the project is FDA regulated and if so, the applicable drug or device regulations that require compliance. The DCI RRCO strongly encourages the research team members to work with them prior to the submission of any documents. The sponsor will usually make the initial determination of FDA applicability but the IRB may request additional information. USAMMDA is available to work with the investigator and the IRB to determine if the FDA should be contacted for guidance or clarification.

## 5.3 Definitions

**510(k) -** The 510(k) is a marketing application to FDA to demonstrate that a new medical device is substantially equivalent to another device that is legally on the market (thus avoiding the need to secure a premarket approval (PMA)). Until FDA has approved a 510(k) application, the device remains investigational and is still subject to Investigational Device Exemptions (IDE) regulations. All IDE regulated studies must be conducted under an abbreviated or approved IDE application [21 CFR 812]. Understanding 510(k) devices helps in applying the IDE exemption category regarding substantial equivalence [21 CFR 812.2(c)(2)].

**Clinical investigation -** Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit (21 CFR 50.3(c))

**Combination products** – includes (21 CFR 3.2(e)):

(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

**Dietary Supplement** - Products (other than tobacco) intended to supplement the diet that bear or contain one or more of the following dietary ingredients:

1. A vitamin;
2. A mineral;
3. An herb or other botanical;
4. An amino acid;
5. A dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
6. A concentrate, metabolite, constituent, extract, or a combination of any ingredient mentioned above.

Further, dietary supplements are products intended for ingestion, are not represented for use as a conventional food or as a sole item of a meal or the diet, and are labeled as dietary supplements. The complete statutory definition is found in section 201(ff) of Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321). In the research context, a dietary supplement may meet the definition of an investigational drug if it meets the definition of a drug as established by the FDA and the intent of the proposed research (e.g., used in the diagnois, cure, mitigation, treatment, or prevention of disease or other condition) 21 USC 321.201(f)(f)

**Drug -** Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals [FD&C Act, sec. 201(g)(1)].

**Emergency Medical Situation** – An instance in which: (1) a single patient has a life-threatening condition; (2) a physician wants to use a drug not approved for general use by the FDA and (3) there is insufficient time to submit a protocol to the IRB.

**Human Subject:** An individual who is or becomes a subject in research, either as a recipient of the test article, or as a control [21 CFR 50.3(g), 56.103(e), 312.3(b)]. A subject may be either a healthy human or a patient [21 CFR 56.102(e)].

**Humanitarian Device Exemption (HDE)** - A premarket approval application submitted to Center for Devices and Radiological Health (CDRH), FDA seeking an exception from the effectiveness requirements of the Food, Drug and Cosmetics Act. [21 CFR 814.3(m)]

**Humanitarian Use Device (HUD)** - A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. [21 CFR 814.3(n)]

**Investigator –** An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

**Investigator Agreement –** An agreement between the investigator and sponsor for an Investigational New Drug (IND) research protocol/study.

**Investigational Device –** A medical device used in a research study to determine the safety and/or effectiveness of the medical device.

**Investigational** or **Experimental Drug** – These are new drugs that have not yet been approved by the FDA or approved drugs that have not yet been approved for a new use, and are in the process of being tested for safety and effectiveness.

**Investigational New Drug (IND) –** An IND is a drug that is available for use only under a "Notice of Claimed Investigational Exemption for a New Drug" approved by the FDA. The use of the term IND may also refer to the associated regulatory application by the sponsor to the FDA.

**Investigational New Drug Application (IND Application) -** A request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans; this is request is usually generated by the sponsor of the research. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics License Application.

**Medical Device** - Any instrument, apparatus, or other similar or related article, including component, part, or accessory, which is:

(a) Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them;

(b) Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals; **or**

(c) Intended to affect the structure or any function of the human body or in animals; **and** does not achieve any of its principal intended purposes through chemical action within or on the human body or in animals and is not dependent upon being metabolized for the achievement of its principal intended purposes.

NOTE: **"Medical device"** includes *in vitro* diagnostic products which are devices that aid in the diagnosis of disease or medical/physiological conditions (e.g., pregnancy) by using human or animal components to cause chemical reactions, fermentation, and the like. A few diagnostic products are intended for use in controlling other regulated products (such as those used to screen the blood supply for transfusion-transmitted diseases) and are regulated as biological products. The IDE regulations apply to clinical investigations of devices to determine safety and effectiveness [21 CFR 812.2(a)].

**Research**: The terms "research," "clinical research," "clinical study," "research protocol", "protocol" and "clinical investigation" are synonymous (21 CFR 56.102(c)) under FDA regulations and activities are research when they involve:

Use of a drug (including an approved drug or an over-the-counter drug) except for the use of an approved drug (approved by the FDA for marketing) in the course of medical practice [21 CFR 312.3(b)];

Use of a medical device except for the use of an approved medical device (approved by the FDA for marketing) in the course of medical practice [Food, Drug and Cosmetic Act 530(g)(3)(a)(i)];

Gathering data that will be submitted to or held for inspection by the FDA in support of an FDA marketing permit for a food, including a dietary supplement that bears a nutrient content claim or a health claim, an infant formula, a food or color additive, a drug for human use, a medical device for human use, a biological product for human use, or an electronic product [21 CFR 50.1(a) or 56.101(a)].

**Sponsor - A** person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

**Statement of Investigator, Form FDA 1572** - An agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.

**Test Article -** Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n)

Additional Food and Drug Administration Definitions and Information

The FDA has additional clarifications and definitions for terms used in human subjects research. Although there are many similarities, there may be subtle differences that require additional regulatory education, guidance or compliance.

**Research**: The terms "research," "clinical research," "clinical study," "research protocol", "protocol" and "clinical investigation" are synonymous (21 CFR 5602(c)) under FDA regulations and activities are research when they involve:

Use of a drug (including an approved drug or an over-the-counter drug) except for the use of an approved drug (approved by the FDA for marketing) in the course of medical practice [21 CFR 312.3(b)];

Use of a medical device except for the use of an approved medical device (approved by the FDA for marketing) in the course of medical practice [Food, Drug and Cosmetic Act 530(g)(3)(a)(i)];

Gathering data that will be submitted to or held for inspection by the FDA in support of an FDA marketing permit for a food, including a dietary supplement that bears a nutrient content claim or a health claim, an infant formula, a food or color additive, a drug for human use, a medical device for human use, a biological product for human use, or an electronic product [21 CFR 50(a) or 5601(a)].

**Human Subject:** An individual who is or becomes a subject in research, either as a recipient of the test article, or as a control [21 CFR 50.3(g), 5603(e), 312.3(b)]. A subject may be either a healthy human or a patient [21 CFR 5602(e)].

Individuals are considered "subjects" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used, or as a control [21 CFR 812.3(p)] in research involving a medical device.

## 5.4 Investigational Drugs

The use of an investigational drug in the conduct of a research protocol may involve a non-FDA approved drug or it may involve an FDA approved drug. In the latter case, it usually relates to a new indication or a new method of introducing the drug into the body (i.e., such as an IV administration of an oral formulation). Investigational drug studies require the use of the Form FDA 1572.

Drug studies use the term "Phase" for each timeline of the drug's development.

Drug studies will provide either a package insert or an investigational new drug brochure (INDB or IDB). The sponsor is responsible for updating the IDB on an at least an annual basis. It provides information obtained during the drug development process, from preclinical to approval or withdrawal.

### 5.4.1 Determining the FDA Status of a Drug

Please refer to the FDA policy available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm119742.htm to determine the FDA status of a drug if there are any questions.

### 5.4.2 IND Requirements

The use of the abbreviation of IND may indicate one of two items. One is the Investigational New Drug Application (IND) which the sponsor submits to the Food and Drug Administration (FDA) to obtain approval to administer an investigational drug or biological product to humans. The FDA grants an IND number to such application if they approve the application.

#### 5.4.2.1 Investigator Responsibilities for Studies in which an IND is Required

An IND is required when the investigator may function as an agent of the sponsor for the conduct of the research study. For example, an investigator (usually a physician) is approached by the sponsor or its representative such as a contact research organization (CRO) or a pharmaceutical sales representative to inquire if they are interested in serving as an investigator on a protocol that the sponsor has already developed. The local investigator agrees to conduct the protocol as written, even if the protocol is different from their preferred standard of care operations. The protocol should be reviewed carefully and these types of operational changes must be implemented to avoid protocol deviations or violations.

Usually IRBs communicate to the sponsor via the investigator and only rarely do they initiate communication directly. The sponsor is the truly the hub of the process as they communicate with the investigator and the FDA.

#### 5.4.2.2 Investigator Requirements for Studies in Which the Investigator is not the IND Holder

The IND may be held by a company, the National Cancer Institute (NCI), the Office of the Surgeon General (OTSG) or others. Their responsibilities are defined in 21 CFR 312**.** The investigator is required to comply with the responsibilities defined in 21 CFR 312 along with completing the following items:

- 
- Provide documentation to the IRB of record from the sponsor or FDA that the IND is active. Note that this documentation should be included in the initial submission for the study. IRB approval will not be granted without this required documentation. This may include a copy of the FDA letter with the IND number.
- Ensure the study is conducted as planned.
- Ensure that the IRB of record review/approval/continuing review and reporting requirements are met
- Protect the rights, safety, and welfare of subjects
    - Maintain control of drugs and keep records for 2 years following the date a marketing application is approved (NOTE: Refer to Chapter 7 Documentation of Human Research Protections for full guidance on record storage.)
    - Obtain informed consent for each subject

- Notify the sponsor and obtain DDEAMC IRB approval before making changes to the protocol
- Report adverse events (AE) to the sponsor and DDEAMC IRB
- Make records available for inspection

### 5.4.3 IND Exemptions

The FDA regulations (21 CFR 312.2(b)) consider clinical investigations involving drug products that are lawfully marketed in the U.S. to be exempt from the requirement for an IND, if all of the following apply:

1. Is not intended to be reported to the FDA as a well-controlled study in support of:
2. New indication
3. Significant change in labeling of the product
4. Significant changes in the advertising of the product
5. Does not involve a new route of administration or dosage level or use in a patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.
6. Is conducted in compliance with:
    a. Required IRB review (21 CFR 56)
    b. Required informed consent (21 CFR 50)
    c. Promotion and charging for investigational product regulations (21 CFR 312.7)

#### 5.4.3.1 Determining Whether a Study Meets IND Exemption Criteria

The FDA 2004 Guidance for Industry in cancer studies and the FDA 2010 Guidance "Determining Whether Human Research Studies Can Be Conducted Without an IND" recommends that investigators and their IRBs determine (based on scientific literature and generally known clinical experience) whether a route of administration or dosage level or use in a patient population significantly increases risks (or decreases the acceptability of the risks). There must be completed documentation regarding the justification whenever a study is determined to be exempt from the IND regulations.

Submit questions cases to the FDA for a "limited review" for a written determination of IND exemption (21 CFR 312.2.(e)) if there are questions regarding the determination of IND exemption.

### 5.4.4 Investigator Responsibilities

Ensure that the investigation is conducted according to the signed agreement, IRB approved protocol, and applicable FDA regulations for protecting the subject's rights, safety, and welfare [21 CFR 312.3(b) by:

- Obtaining an Impact Statement from the Pharmacy for drug studies
- Obtaining informed consent [21 CFR 50, 32 CFR 219];
- Supervising the drug use, accountability, and disposal;
- Maintaining complete and accurate research records including all correspondence, drug records, case report forms (CRF), informed consent documets (ICD, HIPAA Authorizations, adverse effects, any deviations and reporting these as applicable to the DDDEAMC IRB and the sponsor;
- Obtaining continuing review as applicable.

Note that there are several other factors to be discussed during the protocol development phase such as manufacturing the drug, shipping the drug, storage and dispensing of the drug in compliance with state and federal laws, destruction of the drug as well as other legal responsibilities. These types of studies should include extensive discussion with all concerned parties such as the IO, IRB Chair, DCI Chief, HPA, Pharmacy, JAG and others.

#### 5.4.4.1 Investigator Requirements for Studies in Which the Investigator is the IND Holder Serving as Investigator and Sponsor

- A MTF investigator interested in becoming a sponsor-investigator must obtain written authorization from the TSG with justification for acting as a sponsor investigator. See AR 40-7.

### 5.4.5 IRB Responsibilities

The DDEAMC IRB will ensure that at initial and continuing review that these elements are in compliance with:

- IRB registration with the FDA through http://ohrp.cit.nih.gov/file
  - IRB registration must be renewed every 3 years
  - IRB will need to revise its registration for a change in chair and should submit within 90 days of change
- Comply with the FDA regulations for FDA regulated investigational products (21 CFR 50, 56, 312)
- Apply the exemption criteria in determining if a drug study does not require an IND—contact sponsor or FDA if questionable
- Ensure that IRB approved informed consent form (ICF) for FDA-regulated research requires a statement that the FDA may inspect records

### 5.4.6 Expanded Access to Investigational Drugs for Treatment Use - 21 CFR Parts 312 and 316

New Final Rule 13 August 2009 "Expanded Access to Investigational Drugs for Treatment Use" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm172492.htm ) amends the regulation on expanded access. It is intended to improve access to investigational drugs with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies. Under this rule, access will be available to:

- Individual patients, including in emergencies
- Intermediate-size patient populations
- Larger populations under a treatment protocol or treatment IND

Treatment IND and Emergency Use of an IND are examples of expanded access. The DDEAMC IRB's role (usually completed by the IRB Chair) is to:

- Review the protocol and
- Confirm that "safeguards" are in place by the sponsor and investigator and
- Confirm CIRO approval
- Confirm that the patient or legally authorized representative (LAR) has consented.

Expanded access to investigational drugs for treatment use will be available to:

- individual patients, including in emergencies
- intermediate-size patient populations
- larger populations under a treatment protocol or treatment investigational new drug application (IND)

It is intended to improve access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and who may benefit from such therapies

FDA regulations allow for one emergency use of a test article in an institution without prospective IRB review, provided that such emergency use is reported to the IRB within five working days after such use. An emergency use is defined as a single use (or single course of treatment, e.g., multiple doses of antibiotic) with one subject. "Subsequent use" would be a second use with that subject or the use with another subject.

In its review of the emergency use, if it is anticipated that the test article may be used again, the IRB should request a protocol and consent form(s) to be developed so that an approved protocol would be in place when the next need arises. However, in spite of the best efforts of the clinical investigator and the IRB, a situation may occur where a second emergency use needs to be considered. FDA believes it is inappropriate to deny emergency treatment to an individual when the only obstacle is lack of time for the IRB to convene, review the use and give approval. Approval of an IND in an emergency situation is granted only for one-time use. If patient care needs dictate use of the IND at a later time or in another patient, the FDA requires approval of a clinical investigation protocol application by the DDEAMC IRB.

#### 5.4.7.1 Requesting Physician Responsibilities

1) Determine in writing to the IRB that the drug offers an opportunity for patient benefit beyond that of a marketed alternative
2) An IND number must be obtained by contacting the manufacturer and asking for approval to use their IND for a one-time emergency basis. Whenever possible, this should be accomplished by using the drug under a third part IND (usually a manufacturer's IND) with their written approval. If the sponsor cannot provide the physician the IND number because an application is pending FDA approval, the physician should ask for the name and phone number of the medical officer at the FDA who is processing the application. The physician should contact the medical officer for the IND number.
3) If the IND application has not been submitted to the FDA by the manufacturer or sponsor, the physician should contact the FDA, Division of Emergency and Epidemiological Operations, at (301) 443-1240. After regular business hours (holidays, nights and weekends), the physician should contact the FDA at (202) 857-8400.
4) Obtain the patient's voluntary and informed consent to the use of the investigational new drug and document such in the patient's chart. The standard DA Form 522, "Request for

Administration of Anesthesia and for Performance of Operations and Other Procedures", should be used. The sponsoring company's, or manufacturer's, informed consent form will **not** be used for this purpose.

5) Contact the DCI for local clearance and authorization to contact CIRO. Provide both sources with the following information:
   a. Name and diagnosis of patient
   b. Name, dosage, length of use, and source of the drug
   c. IND number for the use of the investigational new drug
   d. Name of the responsible staff physician
6) Document the date and time of local clearance from DCI.
7) Notify the manufacturer/sponsor of the requirement of shipment to the Pharmacy Service.
8) Notify the Pharmacy Service of incoming investigational drugs.
9) The Chief, Clinical Investigation Regulatory Office (CIRO) is the final approval authority for the use of an investigational new drug in a single individual patient upon request from an Army medical facility commander. Contact CIRO for final approval.
10) Submit a memorandum to CIRO through DCI within one working day.
11) The requesting physician will prepare a follow-up written report that includes the outcome of the use of the IND to be submitted to DCI within 10 days of the end of IND treatment or after six (6) weeks of initiating the drug. Include copies of any forms or reports furnished to the drug company manufacturer/sponsor or other non-DA agency in connection with the use of this drug in this patient.

### 5. 4.7.2 DCI Chief and/or RRCO Staff Members Responsibilities

1) The request memorandum is logged into a computerized tracking system by the appropriate Coordinator upon receipt from the PI.
2) The memorandum is reviewed by the DCI Chief or designee as well as the DDEAMC IRB Chair and reported to the IRB at the next convened meeting.
3) The follow-up report is reviewed by the DCI Chief or designee as well as the DDEAMC IRB Chair and reported to the IRB at the next convened meeting.

## 5.5 Investigational Devices

As stated earlier, there are similarities and differences in the regulations regarding device studies and drug studies. Some notable differences are that device studies use:

1) Are classified into a regulatory "class" based on general controls and risk determination
2) A manufacturer's brochure or pamphlet to provide technical and user guidance and background.

Devices in all classes are subject to general controls which require, in part, that companies: (1) register their establishments and list the medical devices they market with FDA; (2) manufacture their devices in accordance with Good Manufacturing Practices; and (3) label their devices in accordance with labeling regulations.

*Class I devices* are subject only to general controls. They typically present the lowest potential for harm and are simpler in design than Class II or Class III devices. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

*Class II devices* are those for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness. In addition to complying with general controls, Class II devices are also subject to special controls identified by the agency, which may include special labeling requirements, performance standards and postmarket surveillance. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

*Class III devices* generally are those for which insufficient information exists to determine that general or special controls are sufficient to provide a reasonable assurance of safety and effectiveness. Examples of Class III devices include replacement heart valves, silicone gel-filled breast implants, and implanted cerebellar stimulators. These require a Pre-Market Approval Program (PMA) to show the device is reasonably safe and effective.

### 5.5 .1 IRB Responsibilities for Review of Medical Device Studies– 510(K), Exemptions and Determinations

A Premarket Notification or 510 K device is usually viewed as a comparison or "me too" device. A 510(k) is required when:

1. Introducing a device into commercial distribution (marketing) for the first time. After May 28, 1976 (effective date of the Medical Device Amendments to the Act), anyone who wants to sell a device in the U.S. is required to make a 510(k) submission at least 90 days prior to offering the device for sale, even though it may have been under development or clinical investigation before that date. If your device was not marketed by your firm before May 28, 1976, a 510(k) is required.
2. A different intended use is proposed for a device which already has commercial distribution. The 510(k) regulation (21 CFR 807[5]) specifically requires a 510(k) submission for a major change or modification in intended use. Intended use is indicated by claims made for a device in labeling or advertising. Most, if not all changes in intended use will require a 510(k). Please note that prescription use to over the counter use is a major change in intended use and requires the submission of a new 510(k).
3. There is a change or modification of a legally marketed device and that change could significantly affect its safety or effectiveness. The burden is on the 510(k) holder to decide whether or not a modification could significantly affect safety or effectiveness of the device. Any modifications must be made in accordance with the Quality System regulation, 21 CFR 820, and recorded in the device master record and change control records. It is recommended that the justification for submitting or not submitting a new 510(k) be recorded in the change control records.

**Changes or modifications to an existing device**

The purpose of a 510(k) is to demonstrate that one device is substantially equivalent to another legally-marketed device. It is not an approval but a clearance from FDA for marketing approval. This could be a device that was on the market prior to 1976 or has since been found equivalent through the 510(k) program. A new 510(k) submission is required for changes or modifications to an existing device, where the modifications could significantly affect the safety or

effectiveness of the device or the device is to be marketed for a new or different indication for use.

When a 510(k) holder decides to modify an existing device, the holder must decide whether the proposed device modification(s) requires submission of a 510(k). It is not FDA's intent that a 510(k) must be submitted for every modification. However, all changes in indications for use require the submission of a 510(k). A change in indication for use includes prescription use to over the counter use. Deciding When to Submit a 510(k) for a Change to an Existing Device[2] provides guidance to 510(k) holders on deciding when to submit a 510(k) for a change to an existing device.

Examples of modifications that *may* require a 510(k) submission include, but are not limited to, the following:

- Sterilization method
- Structural material
- Manufacturing method
- Operating parameters or conditions for use
- Patient or user safety features
- Sterile barrier packaging material
- Stability or expiration claims
- Design

FDA holds that the 510(k) holder is best qualified to determine when modifications to their device could significantly affect safety or effectiveness. Therefore, every modification to the device should be reviewed by appropriate personnel to determine if it affects safety or efficacy. Any design or labeling change to a device should be evaluated and documented in accordance with the 21 CFR 820[3], Quality System regulation. If it is determined that the modification **is not significant**, the basis for this decision should be documented with supporting data in the 510(k) holder's device master file. If it is determined that the modification **is significant**, a new 510(k) must be submitted to FDA.

**Exemptions**
The approval of the DDEAMC IRB is required prior to conducting clinical trials of medical devices. The RRCO staff will review the initial submission to determine if the device is eligible for an exemption under 21 CFR 812 which has seven (7) categories of device investigations that are exempted investigations from IDE Regulations [21 CFR 812.2(c)]:

(1) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(2) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance

with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(3) A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

(i) Is noninvasive,

(ii) Does not require an invasive sampling procedure that presents significant risk,

(iii) Does not by design or intention introduce energy into a subject, and

(iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).

(7) A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

The DDEAMC IRB must review all IDE exempt studies in accordance with the human subject protection regulations before the investigation may begin. Some studies require convened board review, others may be reviewed under expedited procedures (see expedited category number 1.b). When expedited procedures are used, the designated DDEAMC IRB member will determine if the medical device investigation is exempt from the IDE regulations per 21 CFR 812.2(c). If the designated DDEAMC IRB member confirms that the device is exempt from the IDE regulations, the designated DDEAMC IRB member will document finding, and reasons for the finding. Once the device is confirmed as IDE exempt, then a designated reviewer may conduct the review under 21 CFR 56 and 32 CFR 219 if the project is confirmed as no greater than minimal risk.

If the device is not exempt from the IDE regulations, or the expedited reviewer forwards the study to the full IRB, then the protocol will be reviewed by the convened board for the risk determination of the device as well as the risk determination of the project in accordance with 21 CFR 56 and 32 CFR 21.

**Risk Determination of Devices**

In accordance with the Federal Food, Drug, and Cosmetic Act, FDA places all medical devices based on the level of control necessary to ensure safety and effectiveness of the device.

Classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in determining the class to which it is assigned.

### 5.5 .1.1 **Non-significant risk** (NSR)

Some examples of NSR devices include:

- Most daily wear contact lenses,
- Lens' solutions,
- Heel cups,
- Antibacterial surgical garments,
- Incontinence devices,
- Oral training splints, and
- Ultrasonic tooth cleaners.

#### 5.5 .1.1.1 Abbreviated IDE

Non-significant risk (NSR) studies are deemed to have an "approved IDE application" unless FDA has notified the sponsor that approval of an application is required [21 CFR 812.2(b)]. The IRB serves as the FDA's surrogate with respect to review and approval of these studies. The regulations for abbreviated IDEs at Title 21 Chapter 1, Part 812, Section 812 addresses requirements for:

– Labeling
– IRB approval
– Informed consent
– Monitoring
– Maintain records
– Complies with prohibitions against promotion and other practices

### 5.5.2 Significant Risk (SR)

A SR device means an investigational device that:

– Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
– Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
– Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
– Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Examples (not all inclusive) of SR devices are:

- Catheters (other than urological)
- Ventilators
- CPR devices
- TMJ prostheses
- Stents
- Lithotripters
- Sutures and absorbable bandages/materials
- ECT devices

- Extended wear contact lenses
- Pacemakers
- Contraceptive devices
- Most laser systems
- Most hemodialysis systems

#### 5.5.2.1 Full IDE Application

For Significant Risk (SR) studies, an IDE application must be submitted to and reviewed by FDA and IRB approval must be granted before the study can begin. This is usually completed by the sponsor prior to selecting investigators at DDEAMC.

### 5.5.3 Convened IRB Determination of the Risk of the Device

The DDEAMC IRB members should not confuse the concept of minimal risk with NSR device studies because only some NSR studies may qualify as minimal risk. Investigational devices are also classified as by the IRB either posing a significant risk (SR) or non-significant risk (NSR). For medical device studies that do not meet the IDE exemption criteria, the convened IRB will decide whether a study should be approved and determine whether the device study presents a significant risk (SR) or non-significant risk (NSR) by reviewing relevant information:

- Description of the device
- Reports of prior investigations conducted with the device
- Proposed investigational plan and subject selection criteria
- Sponsor's risk assessment and determination
  - The sponsor makes the initial SR/NSR risk determination and presents it to the IRB. The sponsor will notify the IRB if the FDA has already made a SR/NSR determination. The DDEAMC IRB will review the sponsor's evidence and the SR/NSR determination and modifies the determination if the DDEAMC IRB disagrees with the sponsor.
  - The IRB does not revisit the issue of SR/NSR determination if the FDA has already made the SR/NSR determination. The FDA is final arbiter for the SR/NSR determination, and makes the determination when an IDE Application is submitted to FDA or if asked by the sponsor, investigator, or IRB [21 CFR 812.2(b)].
- IDE Application if FDA has cleared, also IDE number

The DDEAMC IRB reviews the total risks of the device study not only the risk of the device under investigation to decide the risk level of the study. If the device is used with a procedure that involves risk, the IRB will consider the risks of the procedure as well as the risks of the device. The determination of SR or NSR is based on the potential harm that may result from participation in the study, including the use of the device

The DDEAMC IRB will document the SR/NSR determination in the IRB minutes:

- Provide reasons for the determination
- Identify the documents relied on to establish the determination
- Notify the investigator and, where appropriate, the sponsor [21 CFR 812.66]

#### 5.5.3.1 IRB Determination of the Risk of the Research Protocol

Some studies that use NSR devices may also be considered minimal risk studies. However, convened Committee review is required for all device studies that do not qualify for expedited review under category 1.b.

Research that uses a device that the IRB has determined to be SR must meet the full IDE requirements including the submission of an IDE application to the FDA prior to IRB approval.

The designation of not-significant risk (NSR) or significant risk (SR) must be made by the convened IRB unless the FDA has made a formal NSR/SR determination that is provided via to the IRB during the submission process.

The DDEAMC IRB will comply with both device and human subject protection regulations [21 CFR 812.60]:

- Conduct review and determine approvability under 32 CFR 219.11
  - Note that making a SR/NSR determination under 21 CFR 812 is not the same as making a risk-level determination under 32 CFR 219. Both determinations need to be made for IDE studies and documented in the IRB minutes.
- For a device study to be eligible for expedited review, it must be:
  - Meet the criteria for an IDE exemption study (NOTE: Not to NSR device studies which are conducted under an abbreviated IDE)
  - Present no more than minimal risk to the subject's and
  - Meet the expedited review category of 1.b.
- Conduct continuing review [21 CFR 812.64, 32 CFR 219.03(b)(4)]

### 5.5.4 Radiation Emitting Devices

These types of studies must undergo additional review by the Radiation Safety Committee. Additional requirements may apply.

### 5.5.5 Humanitarian Use Device (HUD) Background

On June 26, 1996, the FDA issued a final ruling to enforce the provisions of the Safe Medical Devices Act of 1990 regarding humanitarian use devices (HUDs). This regulation became effective on October 24, 1996. A HUD is issued for a specific disease or condition notwithstanding the absence of reasonable assurance of effectiveness [21 CFR 81400(a)(2)]. A HUD device is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year**.** Because a device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations, the FDA developed and published the regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

The regulation provides for the submission of a humanitarian device exemption (HDE) application which is similar to a premarket approval (PMA) application in both form and content, but is exempt from the effectiveness requirements of a PMA. A HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. However, the application must contain sufficient information for the FDA to determine that the device does not pose an unreasonable or

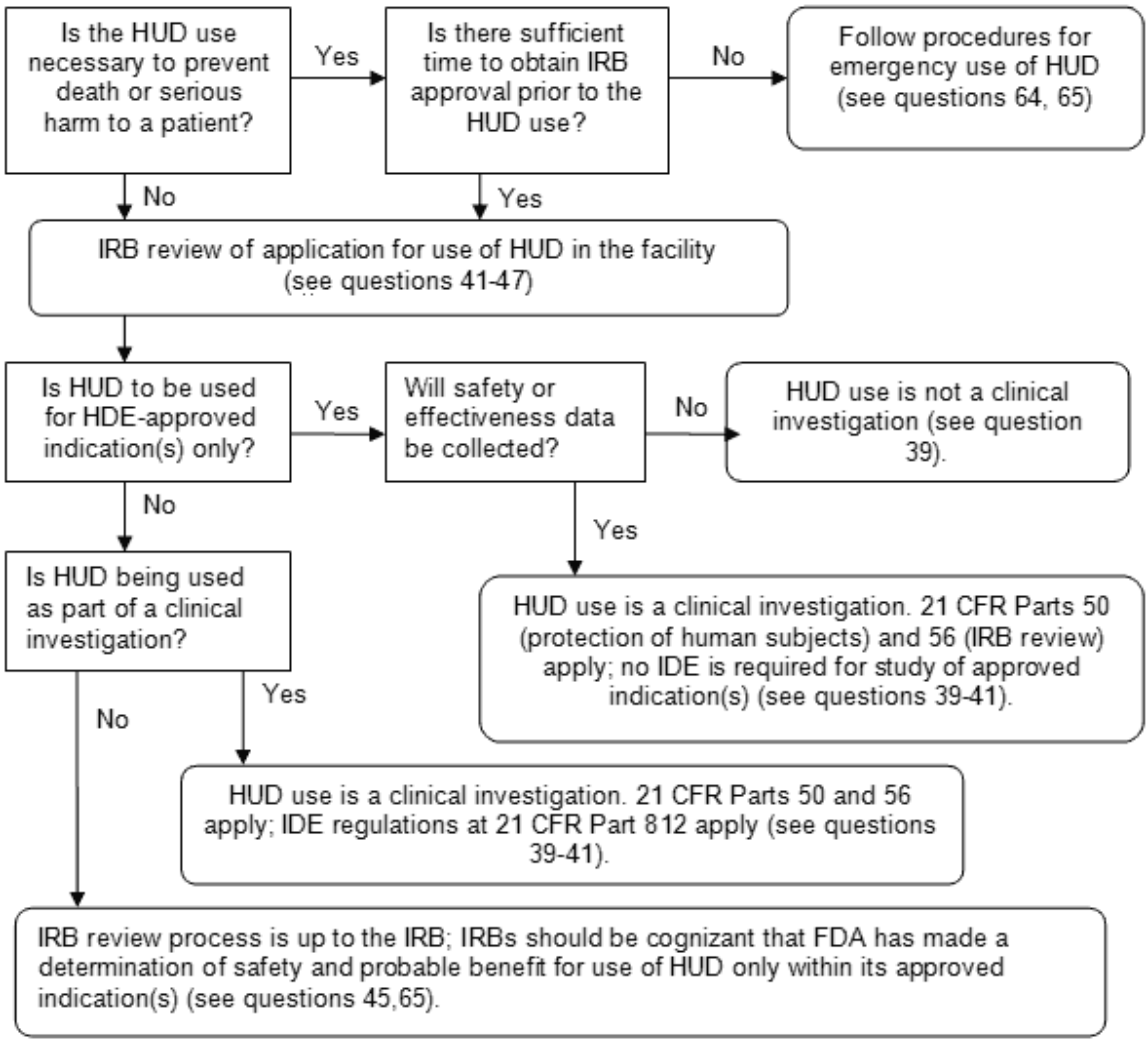
significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market. A Humanitarian Device Exemption (HDE) must be approved [21 CFR 81400(c)] for a HUD to be marketed. Limits are placed on costs that can be charged by the HDE holder.

Once approved the HDE label must state "the effectiveness of this device for this use has not been demonstrated" (21 CFR 81404(b)(4)(ii)) and patients must be informed that effectiveness has not been demonstrated.

- The DDEAMC IRB approval is required before the HUD can be shipped:
  - An emergency exception [21 CFR 81424(a)] is allowed if the DDEAMC IRB approval cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be administered without prior approval by the IRB.
- The physician shall, within five (5) calendar days after the use of the device, provide notification via IRBNet to DDEAMC IRB of such use.
- The IRBNet notification shall include the identification of the patient, the date the device was used, and the reason for the use.
- The FDA recommends obtaining informed consent and submission of a follow up report of patient condition to HDE holder if used outside of approved indication.

There are two HUD uses:
- Treatment **only**
  - For the indication disclosed in approved HDE
  - For another indication – FDA discourages this practice but does not prohibit it
- Research which includes treatment with safety and efficacy data obtained
- All other human subject protection regulations apply
- An IDE must be obtained if the research using HUD is for purpose not approved in HDE

### 5.5.5.1 IRB Responsibilities for Treatment HUD




Even though this is for a treatment purpose and not research, the FDA regulations require IRB approval prior to shipping. The DDEAMC IRB will:

- Approve the use of an HUD [21 CFR 81424(a)] confirming:
  - 21 CFR 5611 approval criteria in conducting a HUD review per FDA recommendations
  - Ensure patient information packet provided to patients
  - Although the use of an Informed Consent Form (ICF) is optional in the Treatment HUD, the DDEAMC IRB requires the use of the ICF including notification that device efficacy has not been demonstrated per FDA recommendations
  - That the use of the HIPAA Authorization is not required [45 CFR 164.512(b)(iii)]
  - Provide Continuing Review and Approval on an annual basis via expedited review as recommended by FDA
- Withdraw IRB approval:
  - A holder of approved HDE shall notify FDA of withdrawal of IRB approval within five (5) working days after being notified. [21 CFR 81424(b)]

When an IRB is deciding whether to approve use of a HUD at a facility (see questions 43-52), its review does not include an SR/NSR determination. As noted above, use of a HUD at a facility to treat or diagnose patients is not a "clinical investigation"; the HUD as such is legally marketed for use within its HDE-approved indication(s).

If an IRB receives a request to review a clinical investigation of a HUD (i.e., collection of safety and effectiveness data), and that clinical investigation concerns the **HDE-approved indication(s)**, then again the IRB does not have make an SR/NSR determination in its review.

The DDEAMC IRB may approve HUD use for:

- General qualifying population
- Individuals meeting specific qualification criteria
- Case-by-case basis

The DDEAMC IRB may limit HUD use based upon:

- Measures of disease progression
- Use and failures of prior treatment modalities
- Specified follow-up precautions and evaluations
- Other criteria as deemed appropriate

The DDEAMC IRB will use the following safety information during its initial and continuing review and may, based on this information, impose additional safety procedures such as:

- Data and Safety Monitoring Board (DSMB) reports
- Research monitor reports
- Serious adverse event (SAE) reporting requirements

### 5.5.6 Investigational Product Control, Record Keeping and Accountability

The DDEAMC pharmacy is responsible for the accountability of investigational drugs or biologics include storing, dispensing, and disposing of the investigational products in accordance with the investigator's written order. The sponsor or manufacturer should send the investigational drug directly to the pharmacy for receipt. This is an important issue if the item requires refrigeration. Please remember to factor in such issues as holiday closings and training holidays for delivery options. The DDEAMC pharmacy must have the following information at a minimum:

- A copy of the investigational new drug brochure (INDB) with information on proper storage, preparation, dosage, indications, contraindications, potential adverse events (AEs)
- PI/AI contact information
- An impact statement

The DDEAMC pharmacy has pre-established inventory accountability procedures with a clear audit trail and these must be maintained. All IND products must have the required labeled statement: "CAUTION: New-Limited by Federal (or United States) law to investigational use."

The DDEAMC pharmacy should have:

- Control of any drug study, regardless of whether it is an IND—such as a commercially available drug used in an IND exempt study
- An electronic record of dispensing, such as CHCS I—allows for identification in patient's medication record and proper labeling

Pharmaceutical sponsored IND studies usually send a representative to inspect and audit records and inventory during their monitoring or auditing visits. The FDA inspectors will also send a representative to inspect and audit records. Any planned visits should be promptly communicated to the appropriate pharmacy staff.

#### 5.5.6.1 Device Accountability

For accountability of devices, the Chief, DCI shall maintain:

- A listing of investigational devices in use within the hospital,
- Their lot or control numbers, and
- The custodians for each device.

## 5.7 References

The following references are provided for information:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.AR 70-25 (Use of Volunteers as Subjects of Research)
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 CFR 219. Protection of Human Subjects. July 1, 2010
5. Title 45 Code of Federal Regulations (CFR) 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Title 21 CFR 11 Electronic Records and Electronic Signature
7. Title 21 CFR 50 Protection of Human Subjects
8. Title 21 CFR 54 Financial Disclosure by Clinical Investigators
9. Title 21 CFR 56 Institutional Review Boards
10. Title 21 CFR 312 Investigational New Drug Application
11. Title 21 CFR 601 Biologics Licensing
12. Title 21 CFR 812 Investigational Device Exemptions
13. Title 21 CFR 814 Premarket Approval of Medical Devices
14. DoD Instruction 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*, November 2011.
15. Clinical Investigation Regulatory Office (CIRO) Memorandum: Clinical Investigation Regulatory office (CIRO) Policy on Human Subjects Protection Regulatory Oversight of the Army Clinical Investigation Program (CIP): Headquarters Level Review Requirements, effective 1 December 2009
16. FDA Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: FDA Frequently Asked Questions About IRB Review of Medical Devices (2006) http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm
17. FDA Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors:

Significant Risk and Non-significant Risk Medical Device Studies (2006) (CD and Notebook)
18. FDA Information Sheets October 1, 1995: Significant Risk and Non-significant Risk Medical Device Studies, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf
19. FDA Guidance for Industry: IND Exemptions for Studies of Lawfully Marketed Drug for Biological Products for the Treatment of Cancer, January 2004, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071717.pdf
20. FDA Guidance for Industry: Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND, October 2010, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175
21. FDA Draft Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers (2008) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm
22. FDA listing of HUD http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm
23. FDA Information Sheets: Frequently Asked Questions: IRB Procedures, FDA Information Sheets: Emergency Use of an Investigation Drug or Biologic, Emergency Use of Unapproved Medical, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm
24. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #1: Institutional Review Board (IRB) Responsibilities and Convened Meeting Procedures

### 6.1.1 Purpose

The purpose of this policy is to provide information about the institutional review board (IRB) as a part of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.1.2 Background

Consistent with 32 CFR 219, the DDEAMC IRB serves as the Human Use Committee for Dwight D. Eisenhower Army Medical Center (DDEAMC) and the military treatment facilities (MTFs) covered under the Department of Defense (DoD) and the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) Assurances. The DDEAMC IRB also has the responsibility to review the scientific merit, adequacy of the research proposals, and establishes priorities for protocol support. The DDEAMC IRB is supported by the Department of Clinical Investigation (DCI), Research Regulatory Compliance Office (RRCO) staff. The DDEAMC IRB membership must fulfill the Department of the Army (DA), DHHS OHRP, and Food and Drug Administration (FDA) requirements for a regularly constituted IRB.

### 6.1.3 IRB Responsibilities

The DDEAMC IRB has three main responsibilities as discussed in detail below.

**Primary IRB Responsibility**

The primary responsibility of the DDEAMC IRB is to protect the rights and welfare of participants involved in human subject research (32 CFR 219.109). In doing so, the IRB:

1. Reviews and monitors human participant research to determine that it is conducted ethically, and in compliance with applicable DoD and federal regulations, applicable State law, DDEAMC's Assurances, agreements for IRB review, and DDEAMC policies and procedures for protecting human subjects.

2. Determines the level of risk associated with subject participation in the research and ensures that those risks are minimized and reasonable in relation to the anticipated benefits.

3. Identifies unique risks associated with involving DoD civilian or military employees as research subjects and minimizes identified risks.

4. Ensures that the selection of participants is equitable and that adequate provisions to protect privacy and confidentiality are maintained.

5. Ensures that research participants will be:
    a. Fully informed about the nature of the research and the risks associated with their participation, and
    b. Promptly provided with any newly acquired information that may affect their well-being or impact their decision to continue participation.

6. Ensures that informed consent will occur and be documented in the approved manner. Informed consent is to be a process continuing throughout the duration of a study.

7. Fulfills these responsibilities by conducting prospective and continuing review of human participant research, including review of the protocol, the informed consent process, procedures used to enroll participants, and any adverse events or unanticipated problems reported to the IRB. Research is not initiated without IRB review and recommendation for approval to the Institutional Official (IO). The IRB will conduct continuing review of approved research at intervals appropriate to the degree of risk, but not less than once per year. Some protocols may be assigned an approval period of less than one year.

8. Reviews protocols at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas except when expedited review procedures are used.

9. Reviews authorizations for research and grants waivers of, or alterations to, such authorization under the privacy regulations promulgated under the Health Insurance Portability and Accountability Act (HIPAA).

10. Promptly reports to the Institutional Official, Clinical Investigation Regulatory Office (CIRO), Army Human Research Protection Office (AHRPO), any reliant IRBs, and other oversight agencies; any unanticipated problems involving risks to subjects or others, and any serious or continuing noncompliance with federal regulations or IRB requirements, and of any suspension or termination of IRB approval as appropriate.

**Second IRB Responsibility**

The DDEAMC does not have a separate scientific review board so the DDEAMC IRB serves as the scientific review board. The second responsibility of the DDEAMC IRB is to review or assess the scientific merit of research protocols.

This will be conducted by a scientific reviewer assigned by the RRCO. This individual may be a member of the IRB or they may be identified as a scientific reviewer from a listing developed by the RRCO staff members as an appointed reviewer. This includes reviewing or assessing the following:

1. Validity of the hypothesis

2. Validity and clarity of the objectives

3. Clarity of the protocol

4. Clinical significance of the protocol
5. Justification for the need of the proposed experiments
6. Clarity of the scientific plan
7. Feasibility of the proposed experiments
8. Availability and expertise by the "experts" who have accepted to help the PI conduct the experiments
9. Justification of the sample size
10. Appropriateness of the statistical design
11. Interpretation of the data
12. Commitment to perform the studies

**Third IRB Responsibility**

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) mandated regulations that govern privacy, security, and electronic transactions standards for health care information including research related information and requires:

1. Standardization of electronic patient health, administrative and financial data.
2. Unique identifiers for individuals, employees, health plans and health care providers.
3. Security standards protecting the confidentiality and integrity of health information.

The Privacy Rule of HIPAA was published on August 14, 2002 and became effective April 14, 2003. The Privacy Rule established privacy standards protecting protected health information (PHI) of an individual, including research activities. These privacy regulations affect researchers and the DDEAMC IRB that serves as the HIPAA privacy board.

The third responsibility of the DDEAMC IRB is to review and assess the plans for the confidentiality of the research data and the privacy of the human subjects enrolled in research protocols. This review is conducted by the primary reviewer assigned by ensuring the presence of a HIPAA Authorization as applicable and that the research study contains appropriate provisions of the privacy of the research data. The DDEAMC HIPAA Privacy Representative is also on the IRB Roster.

### 6.1.4 IRB Authority

The DDEAMC IRB has the regulatory authority to take any action necessary to protect the rights and welfare of human subjects in the DDEAMC research program. Pursuant to DoD regulations at 32 CFR 219.109(a), the DDEAMC IRB has authority to:

1. Recommend approval, require modification to secure approval, or disapprove human subject research;

2. Suspend or terminate ongoing, previously approved research for continued non-compliance with the Common Rule, DoD, DHHS or FDA regulations, or its own findings, determinations, and requirements (32 CFR 219.113);
3. Suspend research that has been associated with unexpected serious harm to subjects;
4. Observe or have a third party observe the consent process and the research.

The Commander as the IO retains the authority to prohibit conduct of research within DDEAMC and its Assurance covered MTFs or by its staff (military, civilians, or contractors) that is deemed to not be in the best interests of the organization or Army (e.g., research that is not consistent with the mission of the Army or DoD; research that would require skills or resources that are not readily available; or research that might result in unacceptable reputational risks).

### 6.1.5 IRB Membership

The composition of the DDEAMC's IRB complies with the requirements of 32 CFR 219.107. Clinicians with a strong generalist background, experience assessing research design and feasibility and a demonstrated commitment to the protection of human subjects are the strongest members of the IRB. The DDEAMC IRB requires at least:

- Five (5) members with varying backgrounds and professional competence and experience appropriate for the type of research reviewed by the IRB and commonly conducted at or by DDEAMC and its Assurance covered MTFs,
- One (1) member whose primary concerns are in scientific areas,
- One (1) member whose primary concerns are in non-scientific areas (for example, lawyers, ethicists, and members of the clergy),
- One (1) member who is not otherwise affiliated with the institution, nor a member of the immediate family of an affiliated individual. (This requirement may be met by appointing a member from an organizational unit not subject to the immediate authority of the DDEAMC Commander.)
- One (1) physician.

The DDEAMC IRB membership will include qualified members:

- Of both sexes (no selection is made strictly on the basis of gender),
- Not consisting entirely of members of one (1) profession,
- Sufficiently diverse relative to race, gender, cultural background, and sensitivity to community attitudes so as to promote respect for the IRB's recommendations and determinations in safeguarding the rights and welfare of human subjects, and

- Who ascertain the acceptability of proposed research in terms of institutional commitments, regulations, applicable law, and standards of professional conduct and practice.

### 6.1.6 IRB Roster

A roster of IRB members and alternates is maintained in DCI that lists the following information for each individual:

a. Name of IRB member.
b. Earned degrees.
c. Scientific status (i.e., scientist or non-scientist).
d. Representative capacity (e.g., children, pregnant women, prisoners, economically disadvantaged, educationally disadvantaged, cognitively impaired adult, etc.).
e. Indications of experience (Provide brief descriptors of all relevant experiences that describe each member's chief anticipated contributions to IRB deliberations, such as professions, life experiences with research or vulnerable populations (Title 45 CFR 46. Protection of Human Subjects, Subparts B, C, or D or FDA 21 CFR 56.111(7)(b), research experiences, IRB experiences, certifications and licensures or other information as appropriate.)
f. Relationship of the member to the organization (e.g., current or former employee, consultant, Board of Directors, volunteer, trainee or student).
g. Affiliation status (Indicate whether the IRB member or any of the member's immediate family is affiliated with the organization).
h. Office (e.g., chair or vice chair).
i. Membership status (e.g., member, alternate member or non-voting. If a member serves *ex officio* indicate whether the member is a voting member).
j. Alternate member for and list the members or class of members for whom the alternate member can substitute.

### 6.1.7 IRB Chair and IRB Vice-Chair

The IRB Chair should have, prior to appointment, a thorough working knowledge of federal regulations for the protection of human subjects, the Belmont Report, and the DDEAMC HRPP and Assurances' terms and requirements.

**Chair Appointment Procedures:**

The DCI may issue an announcement throughout the DDEAMC indicating that qualified staff members may apply for the vacant Chair position of the DDEAMC IRB. Any professional staff may be considered for the positions.

Interested individuals are directed to contact the HPA, Chief, DCI or Deputy Chief, DCI, or the currently serving Chair/Vice Chair to indicate their interest and obtain information about the position. Candidates with previous IRB experience are strongly preferred.

The HPA identifies the most qualified candidates in consultation with a selection panel that may consist of the Chief, DCI or Deputy Chief, DCI, or the currently serving Chair/Vice Chair and makes recommendations to the Commander. The Commander, based on the HPA

recommendation as well as other information available, proceeds with the appointment. The length of service is indefinite.

**Appointment of the Chair:** The DDEAMC Commander, Institutional Official, (IO) appoints the Chair for the Institutional Review Board.

**Term of Service:** The IRB Chair's term of service is usually at three years and may be extended to coincide with his/her military assignment tour length, unless terminated by the Commander.

**Limit of Service:** There is no limit on the number of terms a member may serve.

**Vice-Chair Appointment Procedures:**

The DCI may issue an announcement throughout the DDEAMC indicating that qualified staff members may apply for the vacant Vice-Chair position of the DDEAMC IRB. Any professional staff may be considered for the positions.

Interested individuals are directed to contact the HPA, Chief, DCI or Deputy Chief, DCI, or the currently serving Chair/Vice Chair to indicate their interest and obtain information about the position. Candidates with previous IRB experience are strongly preferred.

The HPA identifies the most qualified candidates in consultation with a selection panel that may consist of the Chief, DCI or Deputy Chief, DCI, or the currently serving Chair/Vice Chair and makes recommendations to the Commander. The Commander, based on the HPA recommendation as well as other information available, proceeds with the appointment. The length of service is indefinite.

**Appointment of the Vice Chair:** The IRB Chair will designate a Vice Chair for appointment by the Commander. The Vice-Chair may serve as Acting Chair in the Chair's absence. Another IRB member, designated by the IRB Chair, can serve as the Acting Chair when the Chair and Vice-Chair are absent from a specific meeting or are recused for a specific action.

**Term of Service:** The term of service for the IRB Vice-Chair service is usually at three years and may be extended to coincide with his/her military assignment tour length, unless terminated by the Commander.

**Limit of Service:** There is no limit on the number of terms a member may serve.

### 6.1.8 Types of IRB Members

There are two (2) types of IRB members on the DDEAMC IRB: Primary and Alternate members.

**Primary IRB Members**

All IRB members regardless of type must possess the appropriate professional competence and experience required to review the type of research reviewed by the IRB and commonly conducted at or by DDEAMC and its MTFs covered under its Assurances.

IRB members are required to be full-time Federal employees (active duty or civilian). The civilian employees may be covered under the Intergovernmental Personnel Act (IPA), or may be consultants consistent with the requirements established by 5 USC 3109.

Procedures for appointment, terms of appointment, length of service, duties and periodic evaluations are outlined later in this chapter.

**Alternate IRB Members**

Each IRB member will have a designated alternate member who serves in the absence of the primary member. The official IRB membership roster must specify which member (or members) the alternate is qualified to replace. Only one member (either primary or alternate) may vote on during an IRB meeting.

Alternate members' qualifications will be comparable to the corresponding primary member's qualifications to ensure that regulatory requirements for IRB composition are met. An alternate for a non-affiliated member should also be unaffiliated with the organization. Alternates for scientific members should have expertise in the same or very similar area as the primary member. Alternates for non-scientific members should also be considered non-scientific.

Alternate members are expected to attend as many meetings as possible to ensure that they remain involved in convened meeting practices and any educational topics. Alternate members will be included in determining or establishing quorum at meetings when their respective primary members are absent, but not when those primary members are present. Alternate members may contribute to the discussion even when they may not vote.

Procedures for appointment, terms of appointment, length of service, duties and periodic evaluations are the same as for regular IRB members and are outlined later in this chapter.

**Periodic Assessment of IRB Members and Research Reviewed**

The HPA and Chief, DCI, with input from the IRB Chair and the Deputy Chief, DCI will conduct an annual assessment to determine if the membership is representative of the types of research that is being reviewed by the DDEAMC IRB. The HPA's duties related to updating the membership roster are outlined in Chapter 1 of this HRPP.

| Member Type | Primary | Alternate |
|---|---|---|
| Appointment Process | The IRB Members are recommended by the IRB Chair and the HPA and appointed by the DDEAMC Commander (IO). | Alternate IRB members are recommended by the IRB Chair and appointed by DDEAMC's Commander (IO). |
| Initial Evaluation of the Proposed Primary Member | The Careline/Department Chiefs nominate qualified individuals. | The individual is representative of the IRB's current needs for representation in regards to the section "IRB Roster" of this chapter. |
| Initial Evaluators | The HPA and Chair review the nominees' credentials to determine if the individual is representative of the | The HPA and Chair review the potential alternate member's qualifications and credentials |

| | | |
|---|---|---|
| | IRB's current needs for representation as well as the appropriate background to serve as an IRB member. | to ensure that the alternate member is equivalent to the primary member. |
| Term of Service | Three (3) years and renewable | Three (3) years and renewable |
| Length of Service | No limit | No limit |

The appointments of the Chair, Vice Chair, and IRB members will be reflected in their duty position descriptions indicating the percentage of their official time to be reserved for IRB related matters.

**IRB Members Compensation**

IRB members are not compensated for their service to the IRB. These are considered "other assigned duties" within the military system. Similarily, no specific liability coverage is provided to IRB members beyond that normally provided as part of governmental service.

**Responsibilities of IRB Members**

IRB membership requires members to attend scheduled and emergency ad hoc meetings. Members will be required to devote several hours per month in preparation for and to attend the IRB meetings. Specific membership responsibilities include:

**Educational Training:**

- Attend the New Member Orientation with the HPA to include matching the new member to a seasoned member for at least two meetings and become familiar with the web addresses of information related to human subjects protection
- Complete the required IRB member training (Chapter 4: Required Education and Training Matrix) within thirty (30) days of their New Member Orientation session.
- Develop an understanding of the ethical principles and regulations for the protection of research subjects
- Participate in continuing education in the field such as the annual Public Responsibility in Medicine & Research (PRIM&R) conferences on a prioritized basis or the numerous human use seminars and IRB conferences held by the National Institutes of Health (NIH) and the Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP)
- Engage in professional networking opportunities

**Review and Evaluate Proposed Research**

- Participate in the review and evaluation of new research protocols and ongoing research studies prior to meetings.
- Conduct a thorough review of protocol materials when appointed as a primary reviewer for a study proposal.
- Complete the required worksheets.

- Contact the investigator prior to the meeting to address any questions.
- Determine if the protocol should be removed from the agenda prior to the meeting.
- Be prepared to summarize the study and critique the research as a primary reviewer.

**Scheduled Meetings**

- One regular meeting per month.
- Attend scheduled IRB meetings and be prepared to be an active participant.
- Discuss protocols and items on the agenda within the member's realm of experience.

**Emergency *Ad Hoc* Meetings**

Members may also be requested to attend an emergency *ad hoc* meeting from time-to-time. Every effort will be made to avoid these types of meeting but circumstances may arise over time that requires these types of meetings. In order to ensure a quorum, members are encouraged to remain flexible and make arrangements to attend these meetings.

**IRB Subcommittee Service**

The IRB may establish subcommittees to assist in the overall work associated with the IRB. The subcommittees may address such issues as adverse events, laboratory studies, or individual protocols that require in-depth and rapid attention. The subcommittees may be ongoing or *ad hoc* in nature.

**Removal of Member**

A member of the DDEAMC IRB may be removed by the DDEAMC Commander for:

(a) Failure to perform the duties of an IRB member, including failure to attend at least 70% of the IRB meetings held within any 12-month period;

(b) Conflict of interest (COI) or

(c) Scientific misconduct

### 6.1.9 Advisors

The IRB Chair or HPA may, at their discretion, recruit advisors whose presence at meetings would aid the IRB in conducting its duties. These advisors may take part in all meetings of the IRB, participate in the discussions, and make recommendations, but they may not vote on the decisions. Advisors are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of advisors.

### 6.1.10 Consultants

In addition to regular members, the IRB may use outside experts as needed for adequate review of protocols. These may vary, except:

(a) For FDA related drug studies, two persons licensed to prescribe the drugs must be included in the review process; and

(b) When the protocol involves vulnerable subjects (e.g. prisoners, children or mentally disabled populations IAW Title 45 CFR 46, Protection of Human Subjects, Subparts B,

C, or D or FDA 21 CFR 56.111(7)(b)), who will be at greater than minimal risk, the outside expert must be a person whose primary concern is the welfare of such subjects.

Before providing the consultant with specific information about the study in question, the HPA or Chair will confirm the consultant does not have a conflict of interest.

A written set of questions may be developed for submission to the consultant for issues requiring only simple clarification. The consultant's written response to the questions will be provided to the IRB for review at the time of the full Committee meeting. For issues requiring more than simple clarification, the consultant may also be invited to attend the meeting during the review of that particular study. Consultants may not count toward the quorum or vote. These individuals have access to all documents submitted to the IRB relevant to the specific study under review, participate in the deliberations, and make recommendations on the study, but may not vote. Any documentation provided by the consultant will be included in the study file and the IRB minutes.

### 6.1.11 Conduct of IRB Meetings

The IRB meetings are the primary source of discussion related to each protocol action. Each IRB member has the right to present the specific issues with which they are concerned related to human subjects protection. This section is to provide information on the general schedule and flow of each meeting.

**Frequency of Meetings**
The Institutional Review Board Meetings (IRB) are conducted once a month on the second Thursday of each month. The meetings may be conducted more frequently if necessary as determined by the Chief, Department of Clinical Investigation or the IRB Chief.

**Quorum Requirements**
A simple majority or at least 51% of the voting IRB members must be present in order to establish a quorum. If an IRB member is the Principal Investigator (PI) or Associate Investigator (AI) of a protocol that is discussed at the convened meeting, that member is excluded from the establishment of a quorum. The member must recuse themselves from the meeting and physically leave the room prior to the closed discussion and vote. A majority of the members should be present at all times during the meeting.

**Guest Observer Attendance**
Persons may be permitted to attend DDEAMC IRB meetings as guests under the following conditions:

a. Guest observer attendance is at the discretion of the IRB chair or designee.

b. Guest observer may be asked to leave at any time.

c. Guest observer may not be in attendance during the deliberations relative to a study in which they serve as PI, associate investigator, or key personnel.

d. Guest observer must reveal any conflicts of interest prior to attendance and must excuse themselves if a potential conflict reveals itself.

e. Guest observer must obtain permission from the DCI RRCO staff prior to attending the meeting.

**Guest Observer Procedures for Convened Meetings**
All guest observers attending the DDEAMC IRB shall sign in and may be asked to document the purpose of their visit. They are informed that all proceedings are confidential.

Guest observers do not receive copies of protocol materials but may be allowed to participate during the presentation of a protocol if they were asked to attend in relationship to that protocol. Guest observers will be asked to recuse themselves if:

1. A protocol is discussed that they are involved in either as a research team member or subject or
2. A conflict of interest arises at any time during the meeting.
3. An item is on the agenda for discussion that should be conducted in a closed session (i.e., discussions regarding alleged or actual non-compliance or protected health information (PHI).

**Pre-Meeting Distribution of Documents**
The place and time of the meeting is set forth on the agenda distributed to all IRB members and alternates approximately one week prior to each meeting. DDEAMC IRB members access all protocol documents on IRBNet. Materials are generally distributed approximately one week prior to each scheduled meeting. All required documents, based on type of review, are available to each IRB member (primary and alternate) by accessing the submitted IRBNet package and/or the "Project History" in IRBNet. In addition to the above items, the primary reviewer has access to a copy of the grant if the research is externally funded.

**Motions at the Meeting**

The following motions may be made at the meeting:

a. Approve the protocol without revisions *or*
b. Approve the protocol with specific revisions requiring simple concurrence by the PI, which upon receipt of the required revisions, approval may be granted by the IRB chair or designee under an expedited review procedure *or*
c. Table the protocol with recommendations for substantive revisions, modifications, or expert review *or*
d. Disapprove the protocol.

Protocols that are tabled or disapproved require that the Chair or designee summarize the issues and advise the PI to consider the discussed points and submit a revised protocol for the convened IRB to review.

At the time of each motion, the members will be asked for a show of hands of all in favor, opposed, or abstaining. Members who oppose or abstain will be asked to state a reason for their vote for the written record.

**Conduct of the Meeting**
The IRB Chair presides over the meeting, using the agenda as a guide. The following order is used for conducting the meeting and this information is documented in the minutes:

**1. Establishes the presence of a quorum to include at least one (1) non-scientist member.**

2. **Calls the IRB to Order**.

3. **Introductions** (NOTE: Individuals will be asked to introduce themselves and provide brief information on their background and/or reason for attendance at the meeting):
   a. New members (primary voting or alternates)
   b. New staff
   c. Consultants or advisors
   d. Guests

4. **Reminds all attendees of the requirement to self-identify any conflicts of interest.** No DDEAMC IRB member, consultant or guest may participate in the initial or continuing review of a project in which the individual has a conflicting interest except to provide information as requested by the IRB. Members who have a conflict of interest in any given protocol cannot be counted toward the establishment of the quorum. Any member or guest who also serves a research team member (PI, AI or other role) must recuse themselves from the meeting except as to provide information for the committee. The committee should not initiate discussion or voting on the protocol until the conflicted individual has left the room.

**5. Makes any administrative announcements to include:**
   a. Notifies the attendees of the status of the previous meeting's minutes
   b. Upcoming education/training opportunities and/or a brief description of any education topic for this meeting
   c. New regulations/guidance documents
   d. IRB policy changes with a brief description of any policies under review and IRB decisions to adopt or revise policies
   e. Other miscellaneous discussions

**6. Reviews any old business.**

**7. Introduces new business to include:**

**<u>Continuing reviews of previously approved protocols to be reviewed by the convened IRB</u>**

- Identifies special issues related to each protocol such as vulnerable populations IAW Title 45 CFR 46, Protection of Human Subjects, Subparts B, C, or D or FDA 21 CFR 56.111(7)(b), or information previously available to the Chair or HPA, etc., to ensure that all additional protections are noted during the review. The committee will carefully consider the added protections under the regulations for vulnerable populations (including children, pregnant women, neonates and fetuses, etc.). The chair will ensure that the substance of the discussion is fully documented in the minutes.

- Assures that the protocol includes necessary IND/IDE information and that FDA regulations have been appropriately followed, as applicable.
  - The Chair will request the committee's decision on significant risk (SR) or non-significant risk (NSR) determinations on IDE exemption device studies.
- Identifies the primary reviewer to present their review
    - The reviewer addresses any reports from the research team of:
        - Deviations
        - Reportable events to include deviations, adverse events, unanticipated problems involving risks to subjects or others
        - Subject enrollment to include dropped, withdrawn, screen failures, etc.
        - Findings of the data safety monitoring committee or board as well as any research monitor reports
- Upon completion of the primary reviewer's presentation, the Chair asks for any discussion regarding the:
  - Scientific merit or study design issues
  - Completeness, accuracy and understandability of the research informed consent form and process
      - The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent or waive the requirement of HIPAA authorization.
  - Determines if the level of risk has changed from the previous review based on this continuing review, as applicable.
- Confirms that the frequency of continuing review as determined by the level of risk is still applicable. High risk studies, particularly those involving new experimental therapies or devices, may be considered for review more than annually.
- Determine whether additional monitoring of the research is necessary for greater than minimal risk (GTMR) protocols.
- Determine level of review for next continuing review (CR) as eligible for expedited review or the requirement for convened board review
- Any controverted issues
- Calls for the motion upon completion of the discussion/comments to:
    - Approve the protocol without revisions or
    - Approve the protocol with specific revisions requiring simple concurrence by the PI, which upon receipt of the required revisions, approval may be granted by the IRB chair or designee under an expedited review procedure or
    - Table the protocol with recommendations for substantive revisions, modifications, or expert review or
    - Disapprove the protocol.
        - Note that the use of "table" or "disapprove" motions require the Chair or designee to summarize the issues and advise the PI to consider the discussed points and submit a revised protocol for the convened IRB to review.
- Calls for a second and then for a show of hands of all in favor, opposed, or abstaining. Members who oppose or abstain are asked to state a reason for their vote for the

written record. The total number of votes is always to equal the total number of voting members present for the vote. The vote is recorded as follows:

- The total number of votes
- The number of members who vote for the action recommended;
- The number of members who vote against the action recommended;
- The number of members who abstain from voting.
- In addition to the votes, the following are recorded:
  - The number and names of members who leave the room for reasons of conflict of interest (i.e., recused);
  - The number and name of members who are present at the meeting, but who are not present in the room when the vote is called.

**New protocol amendments of previously approved protocols to be reviewed by the convened IRB**

- Identifies special issues related to each protocol such as vulnerable populations IAW Title 45 CFR 46, Protection of Human Subjects, Subparts B, C, or D or FDA 21 CFR 56.111(7)(b), or information previously available to the Chair or HPA, etc., to ensure that all additional protections are noted during the review. The committee will carefully consider the added protections under the regulations for vulnerable populations (including children, pregnant women, neonates and fetuses, etc.). The chair will ensure that the substance of the discussion is fully documented in the minutes.
- For FDA regulated research, assures that the protocol includes necessary IND/IDE information and that FDA regulations have been appropriately followed, as applicable.
  - The Chair will request the committee's decision on significant risk (SR) or non-significant risk (NSR) determinations on IDE exemption device studies.
- Identifies the primary reviewer to present their review
- Upon completion of the primary reviewer's presentation, the Chair asks for any discussion regarding the proposed changes in the amendment request to include:
  - Scientific merit or study design issues
  - Completeness, accuracy and understandability of the research informed consent form and process
    - The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent or waive the requirement of HIPAA authorization.
  - Determines if the level of risk has changed from the previous review based on this amendment, as applicable.
- Confirms that the frequency of continuing review as determined by the level of risk is still applicable. High risk studies, particularly those involving new experimental therapies or devices, may be considered for review more than annually.
- Determine whether additional monitoring of the research is necessary for greater than minimal risk (GTMR) protocols.
- Any controverted issues
- Calls for the motion upon completion of the discussion/comments to:

  - Approve the protocol amendment without revisions or
  - Approve the protocol amendment with specific revisions requiring simple concurrence by the PI, which upon receipt of the required revisions, approval may be granted by the IRB chair or designee under an expedited review procedure or
  - Table the protocol amendment with recommendations for substantive revisions, modifications, or expert review or
  - Disapprove the protocol amendment.
    - Note that the use of "table" or "disapprove" motions require the Chair or designee to summarize the issues and advise the PI to consider the discussed points and submit a revised protocol for the convened IRB to review.
- Calls for a second and then for a show of hands of all in favor, opposed, or abstaining. Members who oppose or abstain are asked to state a reason for their vote for the written record. The total number of votes is always to equal the total number of voting members present for the vote. The vote is recorded as follows:
  - The total number of votes
  - The number of members who vote for the action recommended;
  - The number of members who vote against the action recommended;
  - The number of members who abstain from voting.
  - In addition to the votes, the following are recorded:
    - The number and names of members who leave the room for reasons of conflict of interest (i.e., recused);
    - The number and name of members who are present at the meeting, but who are not present in the room when the vote is called.

**New protocols to be reviewed by the convened IRB**

- Identifies special issues related to each protocol such as vulnerable populations IAW Title 45 CFR 46, Protection of Human Subjects, Subparts B, C, or D or FDA 21 CFR 56.111(7)(b), or information previously available to the Chair or HPA, etc., to ensure that all additional protections are noted during the review. The committee will carefully consider the added protections under the regulations for vulnerable populations (including children, pregnant women, neonates and fetuses, etc.). The chair will ensure that the substance of the discussion is fully documented in the minutes.
- Assures that the protocol includes necessary IND/IDE information and that FDA regulations have been appropriately followed, as applicable.
  - The Chair will request the committee's decision on significant risk (SR) or non-significant risk (NSR) determinations on IDE exemption device studies.
  - Identifies the primary reviewer to present their review
- Upon completion of the primary reviewer's presentation as documented in the primary reviewer's worksheet, the Chair asks for any discussion regarding the:
  - Scientific merit or study design issues
  - Completeness, accuracy and understandability of the research informed consent form and process

    - The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent or waive the requirement of HIPAA authorization.
  - Identifies the level of risk, as applicable.
  - Identifies the frequency of continuing review as determined by the level of risk, as applicable. High risk studies, particularly those involving new experimental therapies or devices, may be considered for review more than annually.
- Determine whether additional monitoring of the research is necessary for greater than minimal risk (GTMR) protocols.
- Any controverted issues
- Calls for the motion upon completion of the discussion/comments to:
  - Approve the protocol without revisions or
  - Approve the protocol with specific revisions requiring simple concurrence by the PI, which upon receipt of the required revisions, approval may be granted by the IRB chair or designee under an expedited review procedure or
  - Table the protocol with recommendations for substantive revisions, modifications, or expert review or
  - Disapprove the protocol.
    - Note that the use of "table" or "disapproval" motions require the Chair or designee to summarize the issues and advise the PI to consider the discussed points and submit a revised protocol for the convened IRB to review.
- Calls for a second and then for a show of hands of all in favor, opposed, or abstaining. Members who oppose or abstain are asked to state a reason for their vote for the written record. The total number of votes is always to equal the total number of voting members present for the vote. The vote is recorded as follows:
  - The total number of votes
  - The number of members who vote for the action recommended;
  - The number of members who vote against the action recommended;
  - The number of members who abstain from voting.
  - In addition to the votes, the following are recorded:
    - The number and names of members who leave the room for reasons of conflict of interest (i.e., recused);
    - The number and name of members who are present at the meeting, but who are not present in the room when the vote is called.

**Reports of serious or continuing non-compliance, as applicable**

- Reviews **initial** report, as applicable
  - Determines if additional investigation is necessary and if so, assigns a responsible individual.
  - Determine whether additional monitoring of the research is necessary for greater than minimal risk (GTMR) protocols.
- Reviews **follow-up** reports, as applicable

- Determines if additional investigation is necessary and if applicable, requests additional information
- Determines the level of non-compliance
- Confirm reporting to applicable federal authorities
- Provides information from federal authorities, as applicable
- Recommends outcomes which may include up to suspension or termination of IRB approval and it will include a statement of the reasons' for the IRB's actions.
- If suspended or terminated by the IRB, a memorandum will be sent to the PI, department chief, Commander, sponsor (as appropriate including DHHS and MRMC), and CIRO
- The PI is responsible for notifying the subjects.

**Acknowledgements by the convened IRB of receipt of information such as:**

- Data safety and monitoring reports
- Protocols that were reviewed via the expedited review procedure
  - New
  - Amendments
  - Continuing reviews
- Protocols that were closed

**Unanticipated problems involving risks to subjects or others (UPIRSO)**

- Identifies special issues related to each protocol such as vulnerable populations IAW Title 45 CFR 46, Protection of Human Subjects, Subparts B, C, or D or FDA 21 CFR 56.111(7)(b), or information previously available to the Chair or HPA, etc., to ensure that all additional protections are noted during the review. The committee will carefully consider the added protections under the regulations for vulnerable populations IAW Title 45 CFR 46, Protection of Human Subjects, Subparts B, C, or D or FDA 21 CFR 56.111(7)(b), including children, pregnant women, neonates and fetuses, etc. The Chair will ensure that the substance of the discussion is fully documented in the minutes.
- Identifies the primary reviewer to present their review of the corrective action plan (CAP) or management plan (MP).
- Upon completion of the primary reviewer's presentation, the Chair asks for any discussion regarding the:
  - Scientific merit or study design issues
  - Completeness, accuracy and understandability of the research informed consent form and process
    - The IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent or waive the requirement of HIPAA authorization.

- Determines if the level of risk has changed from the previous review based on this event, as applicable.
- Confirms that the frequency of continuing review as determined by the level of risk is still applicable. High risk studies, particularly those involving new experimental therapies or devices, may be considered for review more than annually.
- Determine whether additional monitoring of the research is necessary for greater than minimal risk (GTMR) protocols.
- Determination of non-compliance to include determinations of :
    - Minor or serious
    - Non-continuing or continuing
- Any controverted issues
- Calls for the motion upon completion of the discussion/comments to:
    - Approve the protocol without revisions or
    - Approve the protocol with specific revisions requiring simple concurrence by the PI, which upon receipt of the required revisions, approval may be granted by the IRB chair or designee under an expedited review procedure or
    - Table the protocol with recommendations for substantive revisions, modifications, or expert review or
    - Disapprove the protocol.
        - Note that the use of "table" or "disapprove" motions require the Chair or designee to summarize the issues and advise the PI to consider the discussed points and submit a revised protocol for the convened IRB to review.
- Calls for a second and then for a show of hands of all in favor, opposed, or abstaining. Members who oppose or abstain are asked to state a reason for their vote for the written record. The total number of votes is always to equal the total number of voting members present for the vote. The vote is recorded as follows:
    - The number of members who vote for the action recommended;
    - The number of members who vote against the action recommended;
    - The number of members who abstain from voting.
    - The total number of votes
    - In addition to the votes, the following are recorded:
        - The number and names of members who leave the room for reasons of conflict of interest (i.e., recused);
        - The number and name of members who are present at the meeting, but who are not present in the room when the vote is called.

**Approval Requirements**

A majority present must approve each action taken during the convened meeting. The majority for the DDEAMC IRB attendance was defined earlier in this chapter.

### 6.1.12 Minutes

The compilation and approval process of the IRB minutes is a collaborative effort as noted below. The minutes of the IRB meetings detail the attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining as well as noted recusals and any conflicts of interests; the basis for requiring changes

in or disapproving research; and a written summary of the discussion of controvertedl issues and their resolution.

**DCI Research Regulatory Compliance Office (RRCO) Staff Responsibilities**

- DCI RRCO staff or a contracted designee will record and compile the minutes of IRB meetings.
- A draft of the minutes is prepared within five (5) working days after the meeting. The draft is provided to the IRB Chair, HPA, Senior Research Compliance Specialist for review, editing, and approval.
- Provide the reviewed draft minutes to the members that attended the convened meeting.
- Make corrections as noted
- Include information on IRB findings and actions
- Prepare the signature cover sheet for the IRB minutes, member roster and any other enclosures to accompany minutes for signature by the Institutional Official/Approving Official.
- Post final signed copy of minutes in IRBNet

**IRB Chair/Vice-Chair Responsibilities**

- Review the draft minutes
- Provide edits/correction to RRCO staff
- Approve when possible and notify RRCO staff

**Members who Attended the Meeting Responsibilities for Minutes Review and Approval**

- Review the draft minutes
- Provide edits/correction to RRCO staff
- Approve by electronic vote

**Institutional Official (IO)/Approving Official (AO) Responsibilities**

- Review and approves the hard copy minutes or delegates this duty to an individual who has completed the required human subject protection training
- Notifies support staff to notify DCI RRCO staff for pick up

**Errors Noted After Approval**

Any errors in DDEAMC IRB meeting minutes will be rectified as soon as possible after they are identified. Errors to approve minutes will be corrected by completing a revised document that identifies the corrections made and obtaining all applicable signatures.

### 6.1.13 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.

4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in Title 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in Title 45 CFR Parts 160 and 164.
8. Department of Defense Instruction 3216.02. *Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*. November 8, 2011.
9. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
10. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
11. Code of Federal Regulations: Title 21, Part 45, Institutional Review Board – Food and Drug Administration.
12. "Guidance on Written IRB Procedures," January 15, 2007, downloaded April 29, 2009 from http://www.hhs.gov/ohrp/humansubjects/guidance/irbgd107.htm
13. "Administrative Tasks Before the Meeting," *Institutional Review Board Management and Function*, Elizabeth A. Bankert and Robert J. Amdur, Jones and Bartlett Publishing, 2006.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #2: IRB Review and Recommendations

### 6.2.1 Purpose

The purpose of this policy is to provide information about the levels of institutional review board (IRB) review and the IRB recommendations to ensure compliance with the applicable federal regulations as part of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.2.2 Background

DDEAMC human subject research protocols and modifications to those protocols must be prospectively reviewed by the IRB, except when the modification is necessary to eliminate apparent immediate hazards to subjects. No human subject research may be initiated or continued without verification of exemption or such prospective approval.

The DDEAMC IRB makes recommendations to the Commander/Institutional Official regarding approval. The Commander may then approve or disapprove the research for implementation. Per guidance of 32 CFR 219.112 , the Commander may not approve the research if it has not been recommended for approval by the IRB and may not overturn any stipulations, conditions, or requirements imposed on a study by the IRB. The Commander may, however, impose additional requirements or restrictions on a study under his or her jurisdiction.

### 6.2.3 Levels of Review and Risk

Human subject research protocols are categorized according to the level of IRB review required as follows:

1. May qualify for expedited review, or
2. Must be reviewed by the convened board

Submit a research protocol to the DDEAMC IRB via IRBNet for their review and determination or approval prior to initiating the research. The protocol shall contain a complete description of the planned research, and it shall include provisions for the adequate protection of the rights and welfare of prospective research subjects and insure that any pertinent laws and regulations are observed. Human use protocols that may qualify for expedited review or that will require convened board review will undergo scientific review.

> **Expedited Review**. Research activities that meet the requirements set forth in 32 CFR 219.110 (i.e., is no greater than minimal risk *and* completely falls within the categories published in the November 9, 1998, Federal Register 63 FR 60364-60367; 63 FR 60353-60356 DHHS-FDA list of research eligible for expedited IRB review) may be reviewed by the IRB Chair or designated IRB member, on behalf of the convened IRB.
>
> **Convened Committee Review**. These protocols are scheduled for review at a convened IRB meeting. They may also be referred to as full review.

**Emergency Use of a Drug or Device**. These activities are related to emergency measures and are limited to the use of test articles that, although they require IRB review and approval for use, do not meet the definitions of human subject research. These do not require prospective IRB approval prior to their use but they do require prompt reporting to the IRB and follow-up within a timely manner.

**Level of Risk**

There are two types of risk that can be assigned by the DDEAMC IRB for any protocol involving human subjects research: No greater than minimal risk (NGTMR) or greater than minimal risk (GTMR).

### 6.2.4 Criteria for Approval of Research of Human Subjects

Federal regulations (32 CFR 219.111) set forth the criteria for IRB approval of research of human subjects at initial and continuing review. In order to approve research, the DDEAMC IRB must determine that all of the following requirements are satisfied:

- Risks to subjects are minimized:
    1. By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
    2. Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.
    - In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapy the subjects would receive even if not participating in the research [32 CFR 219.111(a)(2)]. The risks and benefits related to genetic research must also be considered. The risks and benefits may be to the individual or to groups that are representative of the individual subjects. The IRB will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
    - Questions to ask when reviewing the risks and benefits are:
        1. Does the protocol have scientific merit?
        2. Are the risks complete and consistent across all documents?
        3. Are the study procedures aligned with clinical procedures when possible?
        4. Are procedures in place to minimize/mitigate risk?
        5. Are the risks acceptable in relation to potential benefits?
- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research, the setting in which the research will be conducted, the selection criteria and the recruitment procedures.
    - The IRB should be particularly cognizant of the special problems of research involving vulnerable populations IAW 45 CFR 46, Subparts A, B, C, D, E and 21 CFR Parts 56 (as applicable), such as children, prisoners, pregnant women,

mentally disabled persons, or economically or educationally disadvantaged persons. In some situations, military populations are vulnerable populations. The IRB should ensure that additional safeguards are included in the study to protect the rights and welfare of these subjects.

- Questions to ask when reviewing subject selection are:

1. Who are the subjects? Are they vulnerable?
2. Are the subjects appropriate for the research or are they a convenience sample?
3. Are there sufficient numbers available to conduct the research?
4. What are the inclusion/exclusion criteria?
5. Should certain subjects be excluded for safety or scientific reasons?
6. Are there sufficient safeguards in place to protect vulnerable subjects?

- Unless appropriately waived by the IRB as noted in Chapter 10 Informed Consent, the research informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR) and documented in accordance with and to the extent required by 32 CFR 219.116 and 32 CFR 219.117, respectively.
  - Consent process will be sought only under circumstances that:
    - Provide the prospective subject or their representative sufficient opportunity to consider whether or not to participate.
    - Minimize the possibility of coercion or undue influence.
    - Provide information to the prospective subject or representative in language that is understandable to the subject or their representative.
  - Consent form does not:
    - Include any exculpatory language through which the subject or their representative is made to waive or appear to waive any of the subject's legal rights.
    - Does not release or appear to release the researcher, sponsor, institution or its agents from liability or negligence.
  - Questions to ask when reviewing the informed consent process:
    1. Recruitment (Screening):
       - How will subjects be recruited or identified?
       - Who will recruit?
       - Is the data collected prior to informed consent?
    2. Informed Consent Process and Documentation:
       - Are all information sheets, scripts, consent/assent forms included in the submission?
       - What information will be received in advance?
       - Do subjects have adequate time to consider their participation?

- Does the consent process minimize coercion/undue influence?
- Is the consent process adequate to ensure informed decision?
- Does the consent form contain all the required elements of 32 CFR 219.116 to include:

  a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

  (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

  (2) A description of any reasonably foreseeable risks or discomforts to the subject;

  (3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

  (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

  (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

  (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

  (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

  (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. ***When appropriate***, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

- Should the investigator request that the IRB approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

  (1) The research involves no more than minimal risk to the subjects;

  (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

  (3) The research could not practicably be carried out without the waiver or alteration; and

  (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

NOTE: If the overall protocol is GTMR but the screening portion is minimal risk, a waiver can be granted for the screening portion. HIPAA authorization does not need to be waived at this point because the HIPAA rules allow for the review of PHI by members of the covered entity for the

purpose of seeking HIPAA authorization and therefore can be used in the recruitment of subjects.

- When pertinent, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. For protocols that pose GTMR to subjects and involve treatment interventions, the investigator is asked to provide information on plans for data and safety monitoring.
- Issues to confirm and questions to ask when reviewing the safety monitoring plan:
    1. If GTMR, confirm that a research monitor will be appointed.
    2. What is the definition of a SAE? What should be reported, to who and when?
    3. Are the plans for monitoring data adequate to ensure safety? Are there plans for interim analyses? Are there adequate stopping rules?
    4. Is a data safety and monitoring board (DSMB) necessary? If yes, is the membership and role appropriate?
    5. Is there an adequate emergency response plan to address potential adverse events or unanticipated problems?
    6. Should the DDEAMC IRB review the protocol more often than annually?

- When pertinent, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
    1. Questions to ask when reviewing the safety monitoring plan:
    2. Who will have access to the data?
    3. Will protected health information (PHI) and protected individual information (PII) and identifiable data be safeguarded?
    4. How will data be stored and secured?
    5. What are the long term storage plans and/or plans to destroy the data after compilation?
    6. Are identifiers kept to a minimum?
    7. Does the consent form fully address privacy protections?

Investigators must provide the detailed information needed by the DDEAMC IRB to make the determinations required under regulation in the:

- Initial submission (protocol and applicable addenda, advertisements),
- Continuing review,
- And with amendments if research activities change during the conduct of the research.

The DDEAMC IRB protocol submission form and protocol template were designed to elicit information, in sufficient detail, that the IRB needs to review, consider, and evaluate in order to make the determinations required under regulation (32CFR 219.111) and approve research. Additionally, the consent form template has been formatted in such a manner as to include all of the mandatory elements of consent and additional elements of consent.

The DDEAMC IRB reviews and evaluates research on a protocol by protocol basis to ensure that adequate human subjects' protections are in place and determines that regulatory criteria for approval have been met during the initial and continuing review of research. Reviewer worksheets guide the IRB members in their reviews, determinations, and documentation. If the DDEAMC IRB cannot recommend approval of the research and the investigator will be notified and asked to provide additional information:

- If there is insufficient or incomplete information, or
- If the IRB determines that provisions for protecting subjects are not adequate and criteria for approval are not met based upon the information provided.

**Documenting Review of Research**

Documentation that the required criteria for approval were considered and met when the DDEAMC IRB voted to approve the research will be noted in the minutes of the convened meetings. These actions will be supported by the documents submitted by the PI as reviewed and approved by the IRB, including but not limited to, protocol and other documents available in the protocol file. Other documents may include informed consent forms, HIPAA authorizations, advertisements, etc. The reviewer comment sheets will also provide additional documentation. The IRBNet software allows complete access to these documents for reviewers.

### 6.2.5 IRB Actions

The IRB may take one of the actions noted below and will notify the investigator of such actions via IRBNet.

Approval of the protocol without changes. Protocols that do not involve research in human subjects or protocols that receive exempt review do not require any additional approvals and may be implemented upon notification of the determination.

Approval of the protocol with specific revisions requiring simple concurrence by the PI, which upon receipt of the required revisions, approval may be granted by the IRB chair or designee under an expedited review procedure. DDEAMC IRB members are asked to clearly specify the modifications required to secure approval on the reviewer comment sheet or on the documents submitted by the investigator (e.g., consent form) so that the DCI Research Regulatory Compliance Office (RRCO) staff preparing the PI notification letter and meeting minutes has the language determined approvable by the convened IRB.

Table the protocol with recommendations for substantive revisions, modifications, or expert review. The overall goal of the research may be worthwhile. However, if the DDEAMC IRB has determined that it lacks sufficient information about the research to proceed with its review, or has identified substantive clarifications and/or modifications that are needed in order to meet one or more criteria for approval of research. Recommendation of approval is postponed pending subsequent review of the investigator's response at a subsequent convened Committee meeting. The research may not proceed until the convened IRB has approved a revised protocol incorporating all necessary information. Research review may be deferred for reasons unrelated to the PI. Such reasons may include loss of quorum, unavailability of a required member for a thorough review, or the need for outside consultation to assist the DDEAMC IRB.

Disapproval of the protocol. The DDEAMC IRB has determined that the research cannot be conducted at DDEAMC or its MTS covered by its Assurances. This is typically decided when the research has very serious design flaws, lacks scientific evidence to support the proposed research activities, the application is significantly deficient in information or content or subjects will be placed at undue risk. This action must be taken at a convened meeting.

### 6.2.6 Required IRB Decisions

The DDEAMC IRB is required to make several decisions on each action submitted for each individual protocol. These decisions are to be made based on the federal regulations as well as the special expertise of each IRB member.

**Risk Level**

For each new protocol the DDEAMC IRB must determine whether the research presents a NGTMR or GTMR of harm to subjects.

For amendments and continuing research, the IRB must determine whether the risk level has increased, decreased, or remains unchanged. This information will be documented in the minutes.

**Approval Period**

The DDEAMC IRB will recommend approval for human research activities for a specific time interval appropriate to the degree of risk as noted above but not to exceed one year. The approval period usually begins on the date of the convened meeting at which the research was initially recommended for approval or, in the case of expedited review, the date the IRB Chair (or designated reviewer) documents approval in the reviewer comments section of IRBNet.

At the time of initial review, continuing review, review of amendment requests, or review of adverse, unexpected events or unanticipated problems, the DDEAMC IRB may consider a frequency of review more often than once every year. The IRB usually defines the period as a matter of time (e.g., six months), but also may define it by the number of subjects (e.g., review after the first three subjects are tested). The IRB will consider, at least, the following factors to assess whether a period of less than one year is appropriate:

- The research has a high level of uncertainty regarding potential risks, or it is the first time the intervention/interaction has been conducted in humans.
- Significant or frequent adverse events have been observed in similar research at this or other institutions.
- The experience of the principal investigator and other members of the research team in conducting similar research is limited.
- History of non-compliance with this study, the investigator, or collaborators.
- Inexperienced research personnel or limited research support personnel.
- Multiple amendment requests for previously approved research.
- Several unexpected adverse events or other problems for previously approved research
- Any other factors that the IRB deems relevant for the protection of research subjects.

The RRCO assists the IRB in identifying those studies that potentially meet criteria that would require review more frequently than annually and note this to the IRB during the review process.

**Expiration of IRB Approval**

The expiration date is the last day that the research may be conducted unless the DDEAMC IRB approves renewal of the research following continuing review. Note that this may result in some studies having less than a one year term of approval.

**Additional Monitoring**

If, during the initial review of a research protocol, the DDEAMC IRB determines that a study involves only minimal risk, then annual review is sufficient. However, if the IRB determines that a study involves more than minimal risk, the IRB must also determine whether additional monitoring of the research is necessary. Methods of monitoring ongoing research may include, but are not be limited to, site visits, third party verification, observation of the research and/or consent process, interviews with research subjects, and data and safety monitoring.

Monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

**Determining Which Projects Need Verification from Sources Other Than the Investigator**

The DDEAMC IRB may also consider the need for independent verification of data or interpretation of data in cases where, due to the leading edge nature of the research and/or the potentially high risk to subjects, the IRB decides that more than the investigator's report is needed to allow the IRB to make an informed determination with respect to the research.

Consideration is given to:

- Complex projects involving unusual levels or types of risk to subjects
- Projects that are new to the DDEAMC IRB review experience
- Collaborative or multi-site research
- Projects conducted by investigators:
  - Whose qualifications have not been fully vetted;
  - Physical environment is unfamiliar to the IRB members or staff, or
  - Who previously have failed to comply with the required federal regulations or the requirements or determination of the IRB
- Projects where there is concern that changes to protocols have been made without IRB approval, based upon information provided in the continuing review report or from other sources.

In making determinations about independent verification, the IRB prospectively requires that such verification take place at predetermined intervals during the approval period, or may retrospectively require such verification at the time of continuing review.

**Reconsideration/Appeals**

A DDEAMC IRB ruling is not subject to appeal. The DDEAMC IRB ruling of disapproval cannot be overturned by another group such as the Commander. Only the IRB can alter its previous determination. The DDEAMC IRB may, upon request of an investigator or on its own initiative, reconsider any protocol and reverse its own determination or that of a reviewer of an expedited action.

Investigators may request that the DDEAMC IRB reconsider a decision within 60 days of notification. The Principal Investigator (PI) will submit a written report with strong justification to the Department of Clinical Investigation, RRCO, via IRBNet, in person, by fax or by email. The written request must provide adequate reasons or data to support asking the IRB to reconsider its recommendations; or the investigator must show that the research plan has been altered such that it can secure approval.

The DDEAMC IRB will review all appropriate requests. All requests for reconsideration will be forwarded to the convened Committee for final determination. The Investigator may be asked to attend the meeting as well.

### 6.2.7 Approval Notification to Investigators

The RRCO will generate via IRBNet the appropriate memoranda for approval by the IRB Chair or Commander upon subsequent final recommendation for approval of protocols by the convened IRB, the IRB Chair, or designated reviewer.

For protocols that do not requiring headquarters level approval such as those that are exempt, the Commander may approve for implementation following the final IRB recommendation and RRCO confirmation that all other regulatory requirements and policies have been met.

In the case of protocols for human use research that require headquarters level approval, approval for implementation by the DDEAMC Commander occurs only after headquarters approval. The IRB Chair signs the memorandum via IRBNet informing the PI of the final approval after receiving headquarters approval.

Once the research has been approved for implementation by the Commander, RRCO staff uploads the investigator a copy of the approval letter and, when applicable, the approval-stamped informed consent and recruitment documents into the “board documents” area of IRBNet. All consent forms validated by the IRB will have two dates; the “Approved” date, which is the date that the IRB recommends approval, and the “Expires” date. The expiration date is the date set by the IRB for completion of continuing review and recommendation of re-approval of the research. The interval for the approval of any item presented to a convened IRB will be for one year, unless otherwise specified by the IRB. This length of approval may be for less than one year if the IRB determines this to be appropriate based on the level of review and the type of research. A notice of the re-approval date will be included with the implementation memo.

It is the responsibility of the PI to forward a copy of the final protocol and validated materials to collaborators or funding agency, as required.

Continuing review and amendments require DDEAMC IRB approval notifications and use the same process as noted above for each action.

### 6.2.8 Headquarters Level Administrative Review (HLAR) for DDEAMC IRB

DoD Directive 3216.02 requires that DoD-supported human subjects research must receive a Headquarters Level Administrative Review (HLAR) which is called a second-level review. There are two pathways for this review depending on the type of research conducted and the funding source of that research. These two pathways are outlined below based on the office that conducts the HLAR.

**Clinical Investigation Regulatory Office (CIRO) HLAR**

The U.S. Army Medical Research and Materiel Command (USAMRMC) Clinical Investigation Regulatory Office (CIRO) oversees the HQ second level review process for research that is not funded or supported by USAMRMC.

The following categories of human subject research for new protocols must be reviewed and approved by CIRO prior to the protocol implementation:

- FDA regulated (IND/IDE/HUD) protocols
- Protocol requiring a waiver of informed consent or waiver of HIPAA Authorization

CIRO acceptance of continuing review is required for these protocols but the DDEAMC IRB can issue continuing review approval letters to investigators via IRBNet prior to HLAR.

Amendments to the types of protocols as noted above that could potentially increase risk to subjects must be submitted to CIRO for approval prior to implementation.

All other DDEAMC IRB protocols, associated continuing reviews, and amendments must be forwarded to CIRO for review after DDEAMC IRB approval.

**Non-protocol CIRO Approval Required:**

There may be instances that are related to the conduct of research involving human subjects but that are not truly involving human subjects. However, CIRO approval is still required prior to the implementation of the following:

- Emergency/One Time use of an IND/IDE
- CRADA/SOW (This action by CIRO is required even if the protocol is funded by MRMC.)
- Material Transfer Agreements (MTA)

**Human Research Protections Office (HRPO) HLAR**

All protocols that receive funding from MRMC must be reviewed and approved by the USAMRMC Human Research Protections Office (HRPO) for the HLAR and do not require CIRO review and approval although CIRO will be copied on these actions by the DDEAMC IRB.

### 6.2.9 HLAR Process Overview to DDEAMC IRB

**CIRO Process**

Upon notification of the protocol action in IRBNet by the DCI RRCO, the research protocol is assigned to a Human Subjects Protection Scientist (HSPS) at CIRO who conducts a detailed human research subjects protection review of the protocol and supporting documents. This review may require additional input from the DCI or the investigator.

There are two (2) pathways:

- Those that require CIRO HLAR review and filing
- Those that require CIRO HLAR and approval prior to implementation

The HSPS will draft a Memorandum for Record (MFR) itemizing the review findings. The MFR is reviewed and endorsed by one of the CIRO Section Chiefs prior to transmittal. If regulatory or important administrative comments are noted, the coordinator, department chief and IRB chair will be notified. There are basically two (2) types of comments:

  - Educational which may require a change via an amendment or at the time of continuing review or
  - Required regulatory compliance which usually requires a change prior to the protocol being available for approval and release.

Once all CIRO stipulations have been adequately addressed, the DCI will be directed to submit the amended protocol to the IRB for review and approval. Once the IRB has approved the amended protocol, CIRO will distribute an approval memorandum via e-mail. At that time the Commander may approve implementation of the research.

**HRPO Process**

Upon notification of the protocol action in IRBNet, the research protocol is assigned to a Human Subjects Protection Scientist (HSPS) at HRPO who conducts a detailed human research subjects protection review of the protocol and supporting documents. This review may require additional input from the DCI or the investigator.

The HSPS will draft a Memorandum for Record (MFR) itemizing the review findings. The MFR is reviewed and endorsed by one of the HRPO Section Chiefs prior to transmittal to the PI. The PI may be required to revise the protocol or consent forms to meet standards for approval by HRPO.

Once all HRPO stipulations have been adequately addressed, the DCI will be directed to submit the amended protocol to the IRB for review and approval. Once the IRB has approved the amended protocol, HRPO will distribute an approval memorandum via e-mail. At that time the Commander may approve implementation of the research.

### 6.2.10 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.

4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
9. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
10. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
11. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
12. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
13. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
14. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
15. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
16. Email dated 31 July 2012 from LTC Kevin Leary, subject line: Revised CIRO HLAR Policy.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #3 - Research Determinations

### 6.3.1 Purpose

The purpose of this policy is to provide information to all staff members (military, civilian and contractors) of DDEAMC and all of its military treatment facilities (MTF) covered under the Assurances about the determination of research not involving human subjects at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.3.2 Background

**Human Subjects Determination**

It can be difficult to determine the distinction between human subjects research and research that does not involve human subjects. Investigators must contact the DCI RRCO with questions regarding whether an activity constitutes research that involves human subjects. Research that does not involve human subjects does not require IRB review but the Human Protections Administrator or designee will make the determination whether an activity is considered human subjects research based upon the definition outlined in the DDEAMC Human Research Protection Program (HRPP). There are two levels of determination by the HPA or designee:

1. Research that does not involve human subjects
2. Research may be exempt from IRB review and oversight, or

The HPA or designee makes the final determination and if any concerns exist, the HPA or designee will contact Clinical Investigator Regulatory Office (CIRO) for guidance.

### 6.3.3 Definitions

**Exempt Status**. Protocols categorized as Exempt must satisfy the requirements set forth in 32 CFR 219.101 (b). The protocol must meet DDEAMC HRPP ethical standards governing the conduct of research (e.g., acceptable risk-benefit relationship, equitable selection, informed consent, protections of privacy, maintenance of confidentiality, and protections for vulnerable populations).

**Quality improvement –** Activities undertaken solely to inform and improve operations within the hospital

**Research –** Systematic investigation designed to develop or contribute to generalizable knowledge.

**Research not involving human subjects -** Projects that meet the regulatory definition of research but that does not include interaction or intervention with human subjects or individually identifiable data of living human subjects.

### 6.3.4 Responsibilities

**Investigator Responsibilities**

1. Submit a completed DMRN Project Cover Sheet via IRBNet detailing the planned activity.
2. Respond promptly to all DCI RRCO staff inquiries.
3. Do not initiate project until determination is made.

**HPA Responsibilities**

1. The HPA or designee will review the application to determine whether the activities are research and whether activities that are research involve human subjects.
2. Seek assistance as needed to include scientific review from the IRB Chair or DCI Chief.
3. The reviewer will:
    a. Use the HPA Determination Worksheet to guide and document the review.
    b. Request additional information from the principal investigator (PI)/project director (PD) if necessary to make a valid determination.
    c. Make one of the following determinations:
        i. The proposed activity, as submitted, does not meet the definitions of research involving human subjects and may proceed without further IRB review or
        ii. The proposed activity is research involving human subjects and as such, the PI must submit a complete protocol and supporting documents via IRBNet.
    d. The reviewer will determine and document the appropriate level of review in IRBNet.

**DCI RRCO Responsibilities**

1. Document receipt of the Application for Designation of "Not Human Subjects Research" and conduct an administrative review.
2. Draft a determination letter using the appropriate template which includes the basis of the determination and the IRB Chair will sign the letter.
3. Confirm that all required documentation is placed in IRBNet.

### 6.3.4 Resources

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.

5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
9. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
10. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
11. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
12. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.

# HRPP Chapter 6: Institutional Review Board Policies and Procedures

## Policy # 4: Exempt Research

### 6.4.1 Purpose

The purpose of this policy is to define and provide guidance on research protocols that may be eligible for exempt review under the Dwight D. Eisenhower Army Medical Center (DDEAMC) Human Research Protection Program (HRPP).

### 6.4.2 Background

The levels of IRB review are outlined in Chapter 6, Policy #2 IRB Review and Recommendations. This policy provides additional guidance on the Exempt level of review.

### 6.4.3 Definitions

**Coded** - (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

**Individually identifiable health information -** information that identifies the individual, or with respect to which there is a reasonable basis to believe the information can be used to identify the individual."

**De-identified data** - In addition, the Privacy Rule at section 164.514 allows a covered entity to determine that health information is not individually identifiable using either (1) statistical verification as specified in the Privacy Rule or (2) by removing certain pieces of information from each record, as specified in the Privacy Rule, about the individual, relatives, employers, or household members of the individual and having no knowledge that the remaining information could be used alone or in combination with other information to identify the individual. Under the second method of de-identification, in general, unique identifying numbers, characteristics, or codes must be removed if the health information is to be considered to be de-identified unless permitted by the Privacy Rule as a re-identification code.

**Protected health information** – Is a subset of individually identifiable health information

### 6.4.4 Description of Exempt Research

There are certain research activities involving human subjects that are exempt from DDEAMC IRB review and oversight. These research activities pose “no” or at most “minimal risk” to subjects. Federal regulations that apply to exempt status determination include 32 CFR 219.101(b).

### 6.4.4.1 Exempt Criteria from the Human Research Regulations

Research eligible for exemption determination are limited to the categories identified in 32 CFR 219.101(b)(1)-(6). These are the only criteria that are used to determine if a research protocol may be exempt from IRB review. The IRB may determine a research activity to be exempt where the **only** involvement of human subjects will be in one or more of the following categories:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices such as:

    a. Research on regular and special education instructional strategies, or

    b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

    a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

    b. Any disclosure of the human subjects' responses outside the research could reasonably place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

    ***Note:*** *The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information collected is both identifiable and sensitive.*

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph 2 above, if:

    a. The human subjects are elected or appointed public officials or candidates for public office; or

    b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

NOTE: (i) To qualify for this exemption, data, documents, records, or specimens must have been collected before the research project is submitted for review.
(ii) Under this exemption, an investigator (with proper institutional authorization) may inspect private, identifiable records, but may only record information in a non-identifiable manner. The data must be permanently and completely de-linked at the time of extraction. A code may be used to organize data as it is collected. However, the code may not be a means of re-linking the data set to the original data source.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which is designed to study, evaluate, or otherwise examine:

    a. Public benefit or service programs;

    b. Procedures for obtaining benefits or services under those programs;

    c. Possible changes in or alternatives to those programs or procedures; or

    d. Possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies if certain criteria are met to include:

    a. If wholesome foods without additives are consumed; **or**

    b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Neither the DDEAMC IRB nor the Institutional Official (IO) may create a new category of exempt research.

### 6.4.4.2 Privacy Rule

While Title 32 CFR 219, Protection of Human Subjects Regulations and the Privacy Rule pertain to some of the same entities, the scope of coverage of these two regulations differs. The DOD Protection of Human Subjects Regulations apply to all research involving human subjects that is conducted or supported by DOD, unless the research involves one or more of the categories of exempt research described under the DOD regulations at 32 CFR 46.101(b). FDA Protection of

Human Subjects Regulations apply to research related to FDA-regulated products that involves one or more human subjects. The HHS Protection of Human Subjects Regulations apply to all research involving human subjects that is conducted or supported by any component of HHS, unless the research involves one or more of the categories of exempt research described under the HHS regulations at 45 CFR 46.101(b). FDA Protection of Human Subjects Regulations apply to research related to FDA-regulated products that involves one or more human subjects.

Of note, certain research activities involving human subjects that are exempt under the HHS Protection of Human Subjects Regulations may still need to satisfy the requirements of the Privacy Rule and as such, the project description must include information.

### 6.4.5 Research that Cannot be Exempt

Although the exemption criteria can be used to review the research, the actual subject population will also be a determining factor. Research activities that cannot be determined to be exempt because of the additional protection granted by federal regulations are listed below:

1. Exemptions do not apply to research involving prisoners (45 CFR 46 subpart C) or to fetuses, pregnant women, or human in vitro fertilization (45 CFR 46 subpart B).
2. Exemption at 32 CFR 219.101(b)(2), for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (45 CFR 46 subpart D):
    - Except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
3. The exemptions do not apply to FDA regulated research.

### 6.4.6 Deadline for Submission for Exempt from IRB Review Status

All deadlines are noted in Chapter 6, Policy #10 Deadlines for Submission by the Principal Investigator (PI) to the DDEAMC IRB.

### 6.4.7 Authority to Determine Exempt Status

Investigators do not have the authority to make an independent determination that research involving human participants is exempt. All research claimed to be exempt must be reviewed by the designated reviewer, also known as the Exempt Determination Officer (EDO). The designated reviewer is the Human Protections Administrator (HPA), or in the absence of the HPA, the Senior Research Compliance Specialist, the IRB Chair or Vice-Chair, or the Chief or Deputy Chief, DCI.

#### 6.4.7.1 Continuing Education and Training for Designated Reviewer for Exempt Status

The designated reviewer must have a minimum of one year experience or be a Certified IRB Professional (CIP). Additional training will occur with separate reviews for sixty (60) days to determine that the processes are being appropriately followed. The individual will perform independent protocol reviews to determine whether the proposed protocol is qualified for exemption and for determination of HIPAA implications. In reviewing exemption requests, the reviewer must receive enough information from the Investigator to ascertain whether the claimed exemption genuinely applies.

Continuing education will occur via DCO as available as well as ongoing training opportunities offered by Public Responsibility in Medicine and Research (PRIM&R), the DHHS OHRP regional conferences or other educational programs as offered.

### 6.4.8 Process to Determine Exempt Status

An Investigator may request a particular category of exemption, but the final determination of applicability will be made by the IRB. The designated reviewer will review the "Request for Exemption" and will validate or decline the researcher's claim for exemption. The Request for Exemption must meet one of the six specific categories of activities noted in Section 6.4.4. The designated reviewer will document under which category the protocol qualifies and will forward the protocol to the HPA for review and concurrence. The determination that a research activity is exempt from IRB approval will be determined using the Reviewers Checklist for Exempt Research. The final determination must be provided to the Investigator in writing and should include the citation of the specific category justifying the exemption (e.g., 32 CFR 219.101(b)(1-6)).

If the protocol does not qualify for the exempt status based on the independent reviews, the Principal Investigator will be encouraged to submit a complete protocol application.

### 6.4.9 Informed Consent

Exempt research is not subject to federal regulations contained in 32 CFR 219, which include requirements for informed consent. Therefore, if the research is exempt, then "technically" informed consent is not required. However, the designated reviewer may determine that an informed consent form or information related to the research such as letter of explanation may be appropriate. These are determined on a case-by-case basis. Again, this is not required by the federal regulations, but may be the ethical thing to do to ensure the rights and welfare of the subjects is protected. If the research meets exemption criteria, the designated reviewer may make suggestions on how the letter or form can be improved, but will not withhold approval to require revisions unless the study would not be eligible to be exempted without the changes.

### 6.4.10 Reviews and Determinations

**Research Determination as an Exempt Protocol**

Evaluation and determination of exempt status is performed by the HPA or designee. The DDEAMC IRB reserves the right to disallow exemptions that are allowable under federal policy. Determinations on whether a research activity is exempt or non-exempt must be in writing and provide the basis of the decision.

**Privacy Determination**

The Privacy Rule provides that a Privacy Board may act upon requests for waivers and alterations of the Authorization requirement to permit covered entities to use and disclose PHI for research. Please refer to Chapter 6, Policy #12, HIPAA and the Privacy Board.

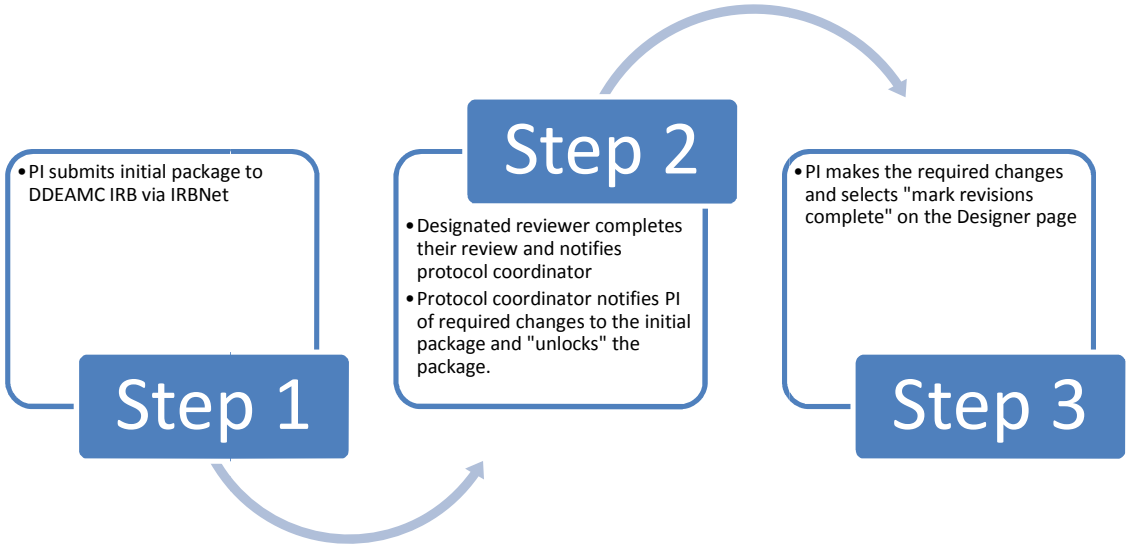
#### 6.4.10.1 Investigator Responsibilities

1. Investigators must submit a new protocol for all research studies involving human participants (i.e., questionnaires, surveys), collection or study of existing data,

documents, records, or specimens. The researcher requesting the waiver or alteration of the Privacy Rule's Authorization requirement from the IRB may be in the best position to adequately describe the PHI to be used and disclosed and would submit this information. The Principal Investigator (PI) should provide all relevant information via IRBNet.

2. After approval by the respective Careline/Department Chief, the PI submits the protocol to the DDEAMC IRB with a complete submission package to include all relevant information via IRBNet.
3. The Investigator is responsible for assuring that the exempt research is carried out in the same ethical manner and with the same participant protections (i.e., confidentiality) as research that is subject to the Common Rule.
4. The Investigator must promptly reply to all requests for revisions and/or clarifications requested by the designated reviewers, when applicable. Requested revisions, changes or additions to the protocol package in IRBNet will generally be accomplished after the DCI RRCO staff "unlock" the protocol package. Upon completion of the designated reviewers requested actions, the investigator must only select the "mark revisions complete" on the Designer page of the package and will **not** submit the package to the DDEAMC IRB. Only "new" packages are submitted to the IRB. Packages "unlocked" for editing are not submitted again.

**IRBNet Submission Process**




### 6.4.10.2 Research Regulatory Compliance Office (RRCO) Responsibilities

1. The protocol coordinator will administratively review the entire study. If the protocol submission package is incomplete, the PI will be notified via IRBNet to revise the

package submission. Refer to Item 3 under 6.4.13.1 Investigator Procedures above for guidance.

2. After completing an administrative review, the protocol coordinator will forward the study to the designated reviewer for ethical and final determination if the study meets the exemption criteria as described at 32 CFR 219.101(b).
3. If the study does qualify for exemption as determined by the designated reviewer without any ethical or safety concerns, the protocol coordinator documents the determination via a determination letter to notify the PI via IRBNet of the following:
   a. The exempt category under which the study qualified.
   b. Date of determination
   c. As applicable, the Privacy Board determination to include:
      - The identity of the approving Privacy Board
      - The date of the waiver or alteration approval
      - A statement that the Privacy Board has determined that all of the specified criteria for a waiver or an alteration were met
      - A brief description of the PHI for which use or access has been determined by the Privacy Board to be necessary in connection with the specific research activity
      - A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures
      - The required signature of the Privacy Board chair or the chair's designee

      As noted, the Privacy Board's documentation of its approval must describe the PHI for which use or access has been determined to be necessary for the research. This would include stating, for example, that the waiver was limited to only certain information in a patient's medical record, instead of the entire record.

4. If the study does NOT qualify for exemption as determined by the designated reviewer, the protocol coordinator notifies the PI via IRBNet and documents why the study is not qualified for exemption. The protocol coordinator will instruct the PI to prepare the protocol for IRB submission.

### 6.4.10.3 Designated Reviewer Responsibilities

1. The appropriate checklist will be used to assist in the review and documentation. The reviewer has the delegated authority to:
   a) Approve a study as meeting criteria for exemption,
   b) Ask for clarification to ensure procedures meet exempt criteria, or
   c) Disapprove the research for exemption. A study that is disapproved for exemption is eligible for submission to the IRB for either a convened or expedited review.
2. Upon initial review of the research project, the designated reviewer may request verification and/or additional information from the Investigator in order to determine

whether exemption is appropriate. This request will be communicated to the Investigator via IRBNet.

3. The designated reviewer will also review in regards to HIPAA requirements. Additional information may be necessary to make this determination. Every effort will be made to include this information with the previous review.
4. There are two outcomes to the review:
   a) The protocol does meet the exemption criteria and is determined to be exempt.
   b) The protocol does not meet the exemption criteria and is not determined to be exempt.
5. The designated reviewer notifies the protocol coordinator of the determination via IRBNet.

### 6.4.11 Documentation and Communications Related to Exempt Review

Documentation and other communications related to the determination of the exempt status is noted in Chapter 7 Documentation of Human Research Protection Activities.

### 6.4.12 Exempt Review Turnaround Time

All turnaround times are noted in Chapter 6, Policy #11 IRB Turnaround Times.

### 6.4.13 Continuing Review

Exempt protocols do not require continuing review but an annual report is required.

### 6.4.14 Amendments/Modifications to Exempt Review Protocols

Information related to modifying or changing the exempt review protocol noted in Chapter 6 Policy #7 Amendments to Approved Protocols for guidance.

Criteria that might change the exempt status of the protocol may include but are not limited to the following:

a. Inclusion of new variables that could place subjects at risk for criminal or civil liability,
b. For retrospective data collection, a request to include data that was obtained after the date of the original exempt protocol submission, or
c. Collection of additional data that could identify the research subjects.

### 6.4.15 Closure of Exempt Review Protocols

Exempt protocols do not require formal closure but an annual update is required.

### 6.4.16 References

The following references are provided for informational purposes:

1. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
2. Department of Defense Instruction 3216.02. “Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research,” November 8, 2011.
3. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.

4. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
5. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
6. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
10. Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP) Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
11. DHHS OHRP Guidance at 45 Code of Federal Regulation (CFR) 46.101(b)(5): Exemption for Research and Demonstration Projects on Public Benefit and Service Programs,
12. DHHS OHRP 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures,
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) "Guidance on Research Involving Coded Private Information or Biological Specimens" available at http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy # 5: Expedited Review Process

### 6.5.1 Purpose

The purpose of this policy is to define and provide guidance on initial review of research that may be eligible under the expedited review categories for the Dwight D. Eisenhower Army Medical Center (DDEAMC) Institutional Review Board (IRB).

### 6.5.2 Background

There are certain research activities involving human subjects that are eligible for the expedited criteria as noted in the federal regulations. These research activities must pose "no more than minimal risk" to subjects IAW 32 CFR 219.102(i). IAW with DoDI 3216.02, when evaluating risk, the phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" in the definition of minimal risk (section 219.102(i) of Reference (c)) shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

### 6.5.3 Definitions

**Coded** - (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

**De-identified data** - In addition, the Privacy Rule at section 164.514 allows a covered entity to determine that health information is not individually identifiable using either (1) statistical verification as specified in the Privacy Rule or (2) by removing certain pieces of information from each record, as specified in the Privacy Rule, about the individual, relatives, employers, or household members of the individual and having no knowledge that the remaining information could be used alone or in combination with other information to identify the individual. Under the second method of de-identification, in general, unique identifying numbers, characteristics, or codes must be removed if the health information is to be considered to be de-identified unless permitted by the Privacy Rule as a re-identification code.

**Expedited** - Only refers to the level of review as defined by federal regulations and does not mean to rush or accelerate the IRB review

**Individually identifiable health information -** information that identifies the individual, or with respect to which there is a reasonable basis to believe the information can be used to identify the individual."

**Protected health information** – Is a subset of individually identifiable health information

### 6.5.4 Expedited Review

It is DDEAMC HRPP policy that the review of all human subject research be conducted in accordance with Department of Defense (DoD) regulations at 32 CFR §219.110; CFR 56.110 Food and Drug Administration (FDA) regulation; and 45 CFR 46.110 Department of Health and Human Services (DHHS).

The expedited review categories are published in 63 Federal Register (FR) 60364-60367, 9 November 1998. The categories listed should not be deemed to be of minimal risk (see above) simply because they are included on the list. Inclusion on the list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human research subjects. Only research that reviewers have found to involve no more than minimal risk **AND** the only involvement of human subjects is in one or more of the categories listed below that may be reviewed by the DDEAMC IRB through expedited review procedures follows.

Categories 1-7 pertain to initial DDEAMC IRB review.

**Category 1.** Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. ***Note:*** *Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.*

b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

**Category 2.** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture, as follows:

a. From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an eight-week period, and collection may not occur more frequently than two times per week; **or**

b. From other adults and children considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight-week period, and collection may not occur more frequently than two times per week.

**Category 3.** Prospective collection of biological specimens for research purposes by noninvasive means. Examples include the following:

a. Hair and nail clippings in a non-disfiguring manner;

b. Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

c. Permanent teeth if routine patient care indicates a need for extraction;

d. Excreta and external secretions (including sweat);

e. Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

f. Placenta removed at delivery;

g. Amniotic fluid obtained at the time of rupture of membrane prior to or during labor;

h. Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

i. Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; and

j. Sputum collected after saline mist nebulization.

**Category 4.** Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, *excluding procedures involving X-rays or microwaves*. Where medical devices are employed, they must be cleared or approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples follow:

a. Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

b. Weighing or testing sensory acuity;

c. Magnetic resonance imaging;

d. Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

e. Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

**Category 5.** Research involving materials (data, documents, records, or specimens) that

a. Have been collected for some other purpose; **or**

b. Will be collected solely for non-research purposes (such as medical treatment or diagnosis).

***Note:*** *Some research in this category may, under some conditions, be exempt from the DoD regulations for the protection of human subjects.*

**Category 6.** Collection of data from voice, video, digital, or image recordings made for research purposes.

**Category 7.** Research on:

a. Individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior); **or**

b. Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

***Note:*** *Some research in this category may, under some conditions, be exempt from the DoD regulations for the protection of human subjects.*

### 6.5.5 Privacy Rule

The Privacy Rule allows the use of expedited review procedures to approve a waiver or alteration of the Authorization requirement. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the HHS or FDA list of approved categories and involves no more than minimal risks. In addition, 32 CRR 219.110, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research protocol, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, since this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB chair or by one or more experienced reviewers designated by the chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure. If the head of the Federal department or agency (or his/her designee) regulating the research has restricted, suspended, terminated, or chosen not to authorize an institution or IRB to use expedited review procedures, the IRB cannot grant waivers or alterations of the Authorization requirement on an expedited basis. Please refer to Chapter 6, Policy #12, HIPAA and the Privacy Board.

### 6.5.6 Procedures

The DoD and FDA regulations permit an IRB to review research through an expedited procedure if the research:

- Constitutes a minor change in previously approved research during the period for which approval is authorized; **or**
- Is classified, not greater than minimal risk, and falls within the categories on the November 9, 1998, DHHS/FDA list of research eligible for expedited IRB review.

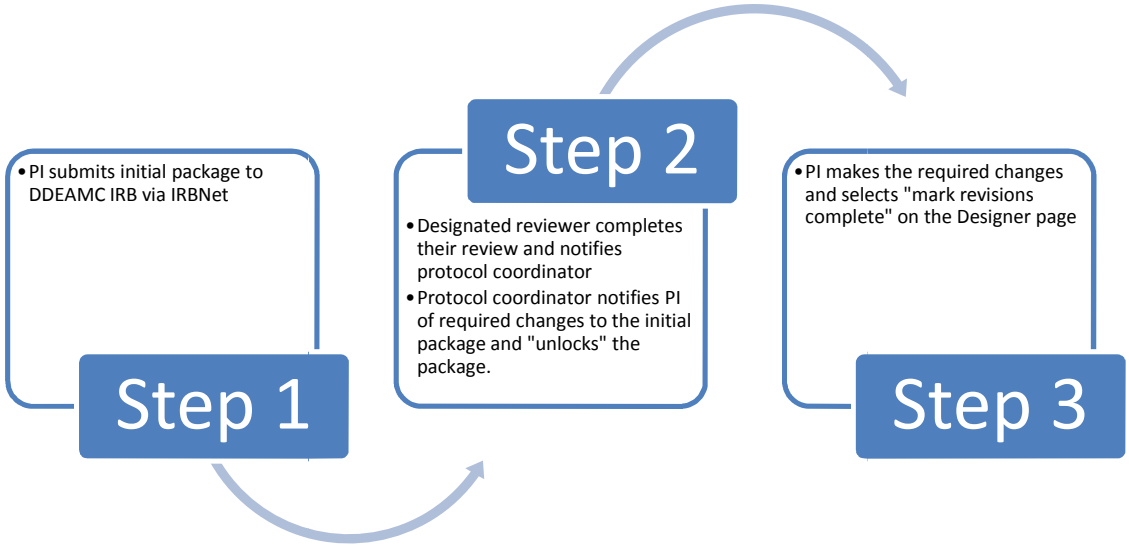
#### 6.5.5.1 Investigator Responsibilities

1. Investigators must submit a new protocol for all research studies involving human subjects (i.e., questionnaires, surveys), collection or study of existing data,

documents, records, or specimens. The Principal Investigator (PI) should provide all relevant information via IRBNet.

2. After approval by the respective Careline/Department Chief, the PI submits the protocol to the DDEAMC IRB with a complete submission package to include all relevant information via IRBNet.
3. The Investigator must promptly reply to all requests for revisions and/or clarifications requested by the designated reviewers, when applicable. Requested revisions, changes or additions to the protocol package in IRBNet will generally be accomplished after the DCI RRCO staff "unlocks" the protocol package. Upon completion of the designated reviewers requested actions, the investigator must only select the "Lock –Revisions Complete" in "Designer" section of the package and will **not** submit the package to the DDEAMC IRB. Only new packages (new protocols) are submitted to the IRB. Packages "unlocked" for editing are not submitted again.

**IRBNet Submission Process**



### 6.5.5.2 Research Regulatory Compliance Office (RRCO) Responsibilities

1. The protocol coordinator will administratively review the entire study. If the protocol submission package is incomplete, the PI will be notified via IRBNet to revise the package submission. Refer to Item 3 under 6.5.6.1 Investigator Responsibilities above for guidance.
2. After completing an administrative review, the protocol coordinator will forward the study to the HPA or trained designee for ethical and scientific review and final determination if the study meets the expedited criteria as described at 32 CFR 219.
3. If the study is approved for expedited review as determined by the Designated Reviewer without any ethical or safety concerns, the protocol coordinator should be mindful that if project is referred for full board to notify the PI to be available during that time to address any questions.

   a. The approval letter will indicate the expedited category under which the study qualified.

   b. All expedited determinations will be reported to the convened IRB at the next scheduled IRB meeting via the meeting agenda.
4. If the study does NOT qualify for expedited review as determined by the HPA, the protocol coordinator notifies the PI via IRBNet and documents why the study is not qualified for expedited review. The protocol coordinator will instruct the PI to prepare the protocol for convened IRB submission.

### 6.5.5.3 Designated Reviewer Responsibilities

1. Use the *"Primary Reviewer Checklist"* to assist in the review and documentation and has the delegated authority to:
   a) Approve a study as meeting criteria for expedited review,
   b) Ask for clarification to ensure procedures meet expedited review criteria, or
   c) Disapprove the research for expedited review. A study that is disapproved for expedited review is eligible for submission to the IRB for convened review.
2. Upon initial review of the research project, the Designated Reviewer may request verification and/or additional information from the Investigator in order to determine whether expedited review is appropriate. The Designated Reviewer will communicate this request to the Investigator via IRBNet.
3. The Designated Reviewer will also review in regards to HIPAA requirements. Additional information may be necessary to make this determination. Every effort will be made to include this information with the previous review.
4. There are two outcomes to the review by the Designated Reviewer:

   a. Approve a study as meeting the criteria for expedited review,

b. Determine that the research as submitted is not eligible for expedited review and it is automatically forwarded for convened committee review.

5. The Designated Reviewer notifies the protocol coordinator of the final determination via IRBNet.

Expedited reviews are performed by the DDEAMC IRB Chair or one or more experienced reviewers designated by the Chair on behalf of the DDEAMC IRB. Designated reviewers may recommend approval, require modifications to secure approval, or forward the protocol to the convened DDEAMC IRB. The designated reviewer may not disapprove any research activity. The research activity may be disapproved only after review by the convened DDEAMC IRB.

Requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review—expedited or convened—utilized by the DDEAMC IRB.

#### 6.5.5.4 Continuing Education and Training for Designated Reviewer for Expedited Review

The DDEAMC IRB Vice-Chair will normally serve as the "Designated Reviewer" although other members may serve if they have sufficient expertise and experience. The Human Protections Administrator (HPA), in consultation with the Chair or Vice-Chair, determines whether an DDEAMC IRB member has sufficient expertise and experience (defined in part by at least six months as a voting member on the DDEAMC IRB) to be an expedited reviewer. The HPA will conduct an initial review of the research to determine if the protocol should be eligible for expedited review.

Additional training will occur with separate reviews for 60 days to determine that the processes are being appropriately followed. The individual will perform independent protocol reviews to determine whether the proposed protocol is qualified for expedited review and for determination of HIPAA implications. In reviewing the request for expedited review, the reviewer must receive enough information from the Investigator to ascertain whether the claimed exemption genuinely applies.

### 6.5.6 Summary of Restrictions for Expedited Review

Expedited review procedures may not be used where identification of the subjects or their responses would easily place them at risk of criminal or civil liability or be damaging to the subjects' reputation, financial standing, employability, etc., unless reasonable and sufficient protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

Expedited review procedures may not be used for classified research.

Additions to and extrapolation from the expedited categories list by the organization or the DDEAMC IRB are not allowed. For example, it is inappropriate to use an expedited review procedure for the initial review of either research that involves minimal risk, but does not appear in the categories of research published in the Federal Register or research that involves greater than minimal risk.

### 6.5.7 Waiver of Informed Consent

Waiver of informed consent may be granted during expedited review if all criteria for such are met. Generally, however, if the investigator will be face-to-face with subjects, informed consent must be obtained. Additional guidance on informed consent process and documentation is available in Chapter 10, Informed Consent.

### 6.5.8 Expedited Review Turnaround Time

All IRB review turnaround times are noted in Chapter 6, Policy #11 Turnaround Times.

### 6.5.9 Continuing Review

Information related to continuing review is contained in Chapter 6, Policy #8 Continuing Review.

### 6.5.10 Amendments/Modifications to Expedited Review Protocols

All information related to amending or modifying an approved protocol is noted in Chapter 6, Policy #7 Amendments.

### 6.5.11 Closure of Expedited Review Protocols

All information related to study closure is noted in Chapter 6, Policy #9 Study Closure.

### 6.5.12 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review

13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 6: Institutional Review Board (IRB) Policies and Procedures

## Policy #6: Convened IRB Review and Recommendations

### 6.6.1 Purpose

The purpose of this policy is to define procedures and operations for items that undergo convened Institutional Review Board ( IRB) review at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.6.2 Background

DDEAMC human subject research protocols and modifications to those protocols must be prospectively reviewed by the IRB, except when the modification is necessary to eliminate apparent immediate hazards to subjects. No human subject research may be initiated or continued without verification of exemption or such prospective approval.

The DDEAMC IRB makes recommendations to the Commander regarding approval. The Commander may then approve or disapprove the research for implementation. However, the Commander may not approve the research if it has not been recommended for approval by the IRB and may not overturn any stipulations, conditions, or requirements imposed on a study by the IRB. The Commander may, however, impose additional requirements or restrictions on a study under his or her jurisdiction.

### 6.6.3 Review by the Convened IRB

DoD regulations at 32 CFR 219.108(b), the Federal Policy (Common Rule) for the Protection of Human Subjects at 45 CFR 46, and FDA regulations at 21 CFR 56 require that the DDEAMC IRB conduct initial and continuing reviews of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for expedited review.

The convened IRB must determine the risk level of all protocols that are reviewed at the convened board meeting. The definition of minimal risk to subjects IAW 32 CFR 219.102(i). IAW with DoDI 3216.02, when evaluating risk, the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” in the definition of minimal risk (section 219.102(i) of Reference (c)) shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain). A protocol may be determined to be greater than minimal risk or no greater than minimal risk at the convened board meeting.

The complete DDEAMC IRB file is available to all members prior to and during the convened meeting via IRBNet. All IRB members will be afforded full opportunity to discuss each research proposal during the convened meeting. A majority of the IRB members as discussed in Chapter

6, Policy #1 must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting as discussed in Chapter 6, Policy #1.

**Privacy Rule**

The Privacy Rule allows the use of convened IRB review. When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review. Please refer to Chapter 6, Policy #12, HIPAA and the Privacy Board.

### 6.6.3.1 Primary Reviewer System

The DDEAMC IRB uses a modified primary reviewer system for actions requiring review by the convened IRB. This "modified" system provides that all IRB members, not just the primary reviewer, have access to the electronic copies via IRBNet of all convened board submissions, including all documents submitted by the PI rather than only a protocol summary and consent form. Primary reviewers are responsible for:

- Conducting an in-depth review of submitted materials and documenting this review using the applicable Primary Reviewer Worksheet,
- Contacting the Investigator prior to the assigned meeting, when necessary, to request additional information and resolve outstanding issues,
- Leading the discussion of the assigned project.

Primary reviewers are assigned protocols by the Chair with consideration of their expertise or interest in the subject area, equal distribution of assignments, and availability to accept the task. The assigned primary reviewer should first review the protocol to determine whether they have the expertise required to evaluate the protocol. If the primary reviewer does not have the appropriate expertise, they must contact the RRCO or the IRB Chair so that they can identify another primary reviewer or a consultant with appropriate expertise.

The primary reviewer must not be involved in the conduct of the proposed research or have any other conflict of interest. If it is not obvious that an IRB member is, in fact, involved in a protocol (e.g., is not listed as a participating investigator), and the protocol is assigned to that member, it is that member's responsibility to inform the RRCO of this situation and to relinquish responsibility for reviewing the protocol.

### 6.6.3.2 IRB Member Review Prior to the Convened Meeting

The DDEAMC IRB members are advised to use the following criteria in making a decision regarding the potential approval of the research protocol:

a. Is the investigation sound?
b. Will the information gained be useful?
c. Is the risk to subjects reasonable in relation to the anticipated benefits?
d. Does the protocol provide sufficient information to justify the risk to benefit ratio?
e. Have the discomforts, inconveniences and risks been minimized?
f. Is the selection of research subjects equitable?
g. Is informed consent being obtained and documented in an acceptable fashion?
h. Are there appropriate provisions to ensure the confidentiality of data and the privacy of the subjects?
i. Are additional safeguards in place to protect vulnerable subject populations?
j. Does the study include a valid plan to monitor side effects?

#### 6.6.3.3 Initial Review Process

1. Upon receipt of a complete DDEAMC IRB submission from the investigator via IRBNet, protocols that do not meet the criteria for exemption or expedited review are placed on the agenda for convened IRB review. Refer to Chapter 6 Policy #10 Deadlines for Submission by the PI to the IRB for all submission deadlines.

2. For all new protocols, the IRB Chair or HPA assigns a primary reviewer with the appropriate expertise to review the topic of the protocol. If there is not appropriate expertise, either an outside consultant will be sought, or the protocol will be rescheduled for review when the expertise is obtained. The primary reviewer is responsible for an in-depth review of all protocol documents. The primary reviewer is strongly encouraged to contact the Principal Investigator prior to the meeting to address and resolve any issues identified during the review.

3. All members are provided access to all research protocol materials via IRBNet to include the scientific review for their consideration prior to the approval of the project. This is usually documented via the Scientific Review Checklist although an email may be substituted if it meets the criterion.

4. Primary reviewers receive a Primary Reviewer Worksheet that must be completed and uploaded to IRBNet prior to the meeting for accessibility to the remaining members. The use of this worksheet is mandatory.

5. Protocols are discussed on an individual basis. Any HRPP member including IRB members or staff who has a conflict of interest (e.g., is involved in the research or has other conflicts) must leave the room during the final discussion and vote. These individuals may be asked questions about the content of the protocol, but must not be present beyond the open discussion and must leave at the time of closed discussion to include IRB deliberations.

6. The primary reviewer presents a brief summary of the study (to include the goals, design, study procedures, and safety procedures), followed by his or her comments. Reviewers are encouraged to use the "Primary Reviewers Presentation Template" and there is a copy of Title 32 CFR 219.111 displayed during the meeting. Following presentation by the assigned primary reviewer, discussion is opened to the convened Committee. All IRB members are afforded full opportunity to discuss each research protocol during the convened IRB meeting.

7. The IRB may invite the principal investigator or other members of the research team to describe the research or answer questions. After general discussion of the protocol, the IRB Chair (or designee) will summarize questions to be posed to the PI. The PI will then be called into the meeting room to answer these questions and any succeeding questions for clarifications. When the Chair (or designee) is satisfied that the questions of the PI have been reasonably examined, he or she will thank the visitors for assisting in the review process and ask them to leave the room.
8. After a final discussion of remaining issues, the IRB calls for any stipulations to be agreed upon and the primary reviewer makes a motion. The motion must include the following:
    a. Determination of Risk Level: The risk level is determined as greater than minimal risk or no greater than minimal risk. The IRB will also determine if a research monitor is required IAW DoDI 3216.02 Enclosure 3, Procedures Section, Item Number 8, Page 24 establishes the requirements for a Research Monitor.

        1. Protocols determined by the DDEAMC IRB to pose greater than minimal risk (GTMR) to subjects, as defined by 32 CFR 219.102(i), shall have an independent Research Monitor (RM) approved by the IRB by name.
        2. For research determined to involve no greater than minimal risk, a research monitor may be identified by an investigator or appointed by an IRB or IO.
        3. There may be more than one research monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.
        4. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.
        5. The IRB must approve a written summary of research monitors' duties, authorities, and responsibilities. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.
            (a) The roles and responsibilities of the research monitors will be established on a study-by-study basis. The duties of the research monitors shall be determined on the basis of specific risks or concerns about the research. The research monitors may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis) and report their observations and findings to the IRB or a designated official.
            (b) The research monitors may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitors shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's

report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

6. The Heads of the OSD and DoD Components may waive the requirement to have a research monitor on a case-by-case basis when the inclusion of a research monitor is not necessary to provide additional protections for human subjects. Requests for such a waiver must be directed to the Army Human Research Protection Office (AHRPO).

b. The required modifications/changes/clarification required to secure IRB approval should be reviewed and noted and it must also be noted if the changes require review by the convened board at the next meeting or if a designated reviewer may provide the review.

c. The frequency of continuing review should be addressed as well as the level of continuing review (covened board or expedited review by a designated reviewer).

d. The motion will be seconded by another voting member for a vote on the motion to occur. The Chair tries to continue discussion until it appears that consensus is reached, but a vote may be called at any time.

e. A vote is taken and recorded by the Recorder for the meeting minutes to include those member for the motion, against the motion or abstaining from the vote.

### 6.6.3.4 After Review Actions

1. In accordance with federal regulations, IRB communications regarding the approval, disapproval, or modifications required to secure approval of research activities are provided in the form of written correspondence via IRBNet. The RRCO is responsible for drafting IRB communications regarding proposed research and any modifications or clarifications required by the IRB as a condition for IRB approval of research. All IRB communications are reviewed and approved by the IRB Chair, designated IRB member, or HPA prior to sending to the Investigator.
2. If the protocol is recommended for approval with stipulations that require simple concurrence by the PI, the RRCO informs the PI of the stipulations and the actions required by the investigator to satisfy the requirements. The designated reviewer or IRB Chair may subsequently review the revised protocol documents on behalf of the IRB under an expedited review procedure if the convened board stipulated certain provisions requiring simple concurrence by the PI. The expedited review of the research will be placed on the agenda and documented in the minutes of the first IRB meeting after the date of reviewer approval.
3. The DCI RRCO coordinates protocol review by committee and primary reviewers. Protocols are not accepted for review unless the protocol submission packet is complete with signatures of assistant investigators, extramural collaborators (if applicable), Careline/Department Chief of PI, completed Impact Statements and DCI Chief.
4. The IRB Chair or HPA assigns the Primary Reviewer for each full review item. IRB Primary Reviewers may meet with investigators to help them better understand the Committee's concerns and to work with the investigator to find acceptable solutions. The IRB Chair may invite investigators to a convened meeting if it is felt their presence may

facilitate the review of a protocol; however, they must leave the meeting prior to the IRB discussing and voting on the protocol.

5. Upon receipt of an investigator's response to IRB communications, RRCO will notify reviewers to maintain access to previously reviewed documents in IRBNet via "Project History" as well as the "Revision" or "Response/Follow-up" package for review in accordance with the prior determination of the IRB.

### 6.6.4 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #7: Amendments to Approved Protocols

### 6.7.1 Purpose

The purpose of this policy is to provide directions regarding the federal requirements for amendments to approved protocols under the purview of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.7.2 Background

Per federal regulations, investigators may not initiate any changes in an approved research activity without prior DDEAMC IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subjects. Changes in research are referred to as amendments, modifications, revisions, or addenda.

### 6.7.3 General Information Concerning Amendments to Approved Protocols

The DDEAMC IRB will review all requests for amendments to previously approved research activities to determine if a change in the risk/benefit ratio of the study has occurred and to ensure that the research will continue to meet regulatory criteria. The following are guidelines for protocol amendments. However, all amendments will be considered in the context of the protocol.

**Minor Amendments that May Qualify for Expedited Review**

IAW 32 CFR 219.110(b)(2) allows that minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 219.108(b). Amendments that receive an expedited review are communicated to the IRB members via the agenda and minutes of the next scheduled IRB meeting. Examples of changes that do not require DDEAMC IRB review include, but are not limited to changes in:

- The addition of research activities that would be considered exempt or reviewed by expedited procedures if considered independent from the main research protocol;
- Improvement in wording or language, correction of typographical errors, or revision of the format of the consent document to agree with requirements of a collaborator's IRB;
- Addition and deletion of qualified key personnel if the responsibilities of that investigator or research associate are appropriately shifted to other personnel, when required;
- Decreasing the number or volume of biological sample collections, provided that such a change does not affect the collection of information related to safety evaluations;

- Alterations in human research participant payment, or liberalization of the payment schedule with proper justification;

An amendment is not necessary when a Cooperative Research and Development Agreement (CRADA) is submitted after the final approval of a protocol or when a pre-existing CRADA is amended, unless the amended CRADA affects the science or risk to the subjects. If scientific review requires additional changes, the investigator will be notified. If the risk to subjects is increased with the amendment, then the protocol may require a change in the level of review from expedited to convened review. Note that a change in the PI to a CRADA will require JAG concurrence.

**Major Amendments Requiring Convened Review**

If a proposed change substantially changes the specific aims or design of the study or significantly alters the risk to benefit assessment, the DDEAMC IRB relied upon to approve the study, the change constitutes a major amendment. When a proposed change in a research study is not minor, then the IRB must review the amendment at a convened meeting, and the AO must approve the changes before they can be implemented. Examples of major amendments may include, but are not limited to, the following:

- Change of risk to subjects
    - Change to inclusion/exclusion
    - Number of subjects
- Study design
- Vulnerable populations (pregnant women, fetuses, neonates, children and prisoners)
- Legally authorized representative (LAR)
- FDA Regulated (IND/IDE/HUD)

Protocol changes may commence upon DDEAMC IRB approval.

**Amendments to Protocols that were Initially Deemed Exempt from IRB Review**

Any proposed or anticipated changes in an exempt study must be approved by the DDEAMC IRB prior to initiating the change. The proposed change (s) will be submitted to the RRCO staff at DCI via IRBNet through an amendment submission. The proposed change must be reviewed and a determination or ruling made on whether the proposed change(s) affect the exempt status. If the modification would remove exempt status, RRCO staff will notify the PI in writing that he or she may withdraw the amendment request and continue the study as previously determined to be exempt or submit the protocol for appropriate DDEAMC IRB review through expedited or convened committee procedures.

Any proposed changes to an exempt study must be submitted to the IRB for review and approval prior to implementation. Certain changes may disqualify the research from exempt status; therefore, all changes in the research plan must be reported to the IRB for review and approval, prior to implementation. Any proposed changes to the approved exempt protocol must be submitted in via IRBNet for an amendment submission prior to implementation. A determination must be made as to whether the requested change(s) affect the protocol's exempt status.

Criteria that might change the exempt status of the protocol may include but are not limited to the following:

a. Inclusion of new variables that could place subjects at risk for criminal or civil liability,
b. For retrospective data collection, a request to include data that was obtained after the date of the original exempt protocol submission, or
c. Collection of additional data that could identify the research subjects.

When an Investigator submits an amendment for an originally exempt study, the designated reviewer will review the amendment to verify that the study still meets criteria for exemption, as described at 32 CFR 219.101(b).

RRCO staff will change the status of the IRBNet amendment package to "Approved" if the designated reviewer determines that the modification would not change the exempt status of the study. If the amendment makes the study ineligible for exempt status, RRCO staff will inform the PI via IRBNet to explain why the study does not qualify for exemption, and provide draft instructions to the Investigator requesting that a complete protocol be submitted for IRB review.

### 6.7.4 Amendment Preparation and Submission Requirements

The approval of an amendment does not change the approval or expiration date of the research activity. The amendment is considered by the IRB to be a component of the research protocol as opposed to the research protocol in whole form. The approval simply approves the modification or amendment to the project and allows the investigators to begin using the modified or new procedures, documents, etc.

**Principal Investigator (PI) Responsibilities at Time of Submission for Amendment**

The PI responsibilities are:

1. Submits the amendment via IRBNet for processing.
2. Ensure each modification of an approved protocol is submitted for IRB review and that the amendment has been approved by the IRB and the AO prior to implementation, unless there are immediate hazards to human research subjects.
3. Ensure the amendment request is submitted sufficiently in advance of planned implementation, to allow for processing and review times.
4. Reply to any requests made by the RRCO staff, the IRB Chair, or HPA or designee in a timely manner until the amendment has been approved, disapproved, or withdrawn.
5. Submit the complete package as outlined below.

**Required Documents in the Package**

Each protocol amendment may require multiple documents to ensure that the IRB has the most complete package on which to determine the level of review as well as the risk involved to subjects or others.

**Revised Protocol Document**

Amendments must be incorporated into the written protocol at the time of continuing review. This practice ensures that there is only one complete protocol with the revision date noted on each page. When approved, the revised protocol, as well as informed consent documents and other dated documents, then supersede the previous ones. The electronic (complete document)

of a tracked changes version and a clean version of the revised protocol must be submitted. ***Note:*** *If the modification is only a change in study personnel, it is not necessary to submit a tracked changes version and only the cover sheet should be changed. Confirm that duties as well as responsibilities, access to data, etc. , are discussed when personnel changes are made.*

**Revised Site Specific Addendum**

This document should be updated at the time of amendment submission.

**Revised Consent Forms and Recruitment Materials**

An updated version of each document changed by the amendment must be submitted via IRBNet. Revised documents must have a new version date. One version of the consent form without highlighting or tracked changes should be provided (for approval date stamping). A tracked changes or highlighted version of the consent form needs to be provided only if there are substantial changes.

**DDEAMC IRB Responsibilities for Amendment Review**

Amendments to research previously approved by the convened IRB may be reviewed by expedited procedures if they meet the following criteria:

1. The modifications do not pose an increased risk to subjects;
2. The modifications constitute a minor change to the previously approved research. To be considered minor, the change should not materially affect the assessment of risks and benefits.

Amendments to research previously approved by the expedited review procedure may be reviewed via expedited procedures if they meet the following criteria:

1. The research continues to pose no more than minimal risk to subjects with the modifications.
2. The modifications involve only procedures that fall within the expedited review categories.

**Protocol Coordinator Responsibilities upon Receipt from the PI**

1. Provide technical assistance to PIs on the required format and documentation for amendments.
2. The protocol coordinator will administratively review the amendment submission. If the protocol submission package is incomplete, the PI will be notified via IRBNet to revise the package submission.
3. After completing an administrative review, the protocol coordinator will forward the study to the HPA or designee or IRB Vice Chair for ethical and scientific review and final determination if the study meets the expedited criteria as described at 32 CFR 219.110(b)(2).
4. Notify the PI via IRBNet of IRB requests for changes or additional information or reasons for disapproval.

**Protocol Coordinator Responsibilities upon Approval Notification**

1. Place notification of expedited review on the next available IRB meeting agenda for amendments determined to be minor and approved by the IRB Chair or designated IRB reviewer.
2. Assure that the applicable IRB review agreements or local IRB approvals for collaborative research are in place prior to release of approval for implementation.

3. For an amendment that requires review by the CIRO, submit a copy of the amendment request, revised protocol documents, and minutes of the relevant IRB meeting for second-level review and approval.
4. Complete and obtain approval signature on the amendment approval memorandum or, if certification of approval is to be provided to other IRBs, prepare implementation approval memorandum for AO's signature.
5. If the approved amendment includes revisions to the consent document, stamp the approved consent document with the IRB approval stamp, approval date, and expiration date.
6. If the approved amendment includes revisions to recruitment materials, stamp the approved documents with the IRB approval stamp and approval date.

**Human Protections Administrator (HPA) or Designee Responsibilities**

The HPA or designee reviews the request and makes an initial determination of the required level of review. If any necessary documents were not provided, the staff will contact the PI via IRBNet and request missing items.

1. Expedited review - The HPA or designee may review and approve research that meets the definition of a minor amendment using expedited procedures. The HPA or designee must:
    - Document that the amendment does qualify for expedited review procedures IAW 32 CFR 219.110(b).
    - Submit a request via IRBNet to the PI for additional information or changes to resolve issues prior to further action;
    - Complete the Determination Worksheet
    - Assign the amendment to the designated reviewer.
2. Convened DDEAMC IRB review - The amendments that are determined by the HPA or designee to not qualify for expedited review because the request includes moderate changes to the protocol or request for changes that negatively alter the risk/benefit for study subjects. These requested amendments must be scheduled for review at the next convened IRB meeting **or**
3. Requires a new research protocol using the criteria as noted below:
    - Significant changes in research objectives
    - Major changes in procedure, method, or organization of the study to include multi-year extensions of ongoing studies.
    - Major changes in the use of experimental subjects
    - Changes in the dosing regime (i.e., amount, number of times, etc.)
    - Any increased risk to subject whether the risks involve physical, psychological, social, economic, confidentiality risks, etc. (i.e., increased number of blood draws, more procedures, adverse events, etc.)
    - Protocols involving vulnerable subjects (adding pediatric subjects to an approved protocol)

4. Determine if there are any impacts on the application of the Privacy Rule on the project and if there are, notify the IRB as the Privacy Board of any concerns.

After the level of review has been determined, the HPA or designee will:

1. Process the review according to the initial review of the research and whether the amendment reflects a major or minor change as outlined below:
    - Changes requested by the PI that meet the criteria for minor amendments will be forwarded along with the appropriate checklist for review and signature by the IRB Chair or designated IRB Reviewer (usually the reviewer of the initial IRB submission).
    - Changes requested by the PI that meet the criteria for major amendments will be forwarded to the Primary Reviewer (usually the Primary Reviewer of the initial review) and all relevant documents ( for example, the amendment, informed consent forms, the most recent Continuing Review and the full protocol) will be posted in IRBNet. The study will be placed on the next available IRB meeting agenda. Access to the full file will be available via IRBNet both during and at least one week prior to the IRB meeting.
    - Changes to exempt research may be approved by the HPA or designee if changes do not change the review level of the study.
2. Forward the amendment, if appropriate, for scientific review.

**IRB Committee Responsibilities for Convened Review**

- When a proposed change in a research study is not minor, the IRB committee reviews the changes at a convened meeting. The IRB approved amendments must receive final approval by the AO before changes can be implemented. The RRCO provides review materials to the members at least one week prior to the meeting. All Committee members will receive and should review these:
    - The amendment request form/memo;
    - All amended information or additional information including the amended protocol, and amended informed consent document if applicable, or the most current informed consent document if not amended;
    - Any additional pertinent material (e.g., questionnaires, advertisements, safety review, health hazard assessment, product literature, published literature);
- The Primary Reviewer completes the appropriate worksheet/checklist presents his or her evaluation of the non-minor amendment to the convened committee for review.
- The IRB is required to review and approve research using the criteria at federal regulations 32 CFR 219. When reviewing modifications to approved research (amendments), the criteria for IRB approval must be met to approve the amendment.
- The IRB (whether individual reviewer or convened committee) should determine how the change may affect the approval criteria. The IRB will review the amendment request in comparison with the approved research study prior to making a determination. The IRB should, in particular, consider the following:

- The type of change (modification vs. addition)
- Effect of the change on level of risk
- Effect of the change on the project's review level or qualification category
- Effect of the change on the overall research project
- Required changes in the consent form
- Effect of the change on subjects' willingness to continue the study
- The need to re-consent currently enrolled subjects

- Based on the review of the amendment submission, the IRB makes the following determinations or motions:
  - Alter the approval period or frequency of continuing review of the amended study.
  - Recommend approval to the AO as submitted, with no changes (or no additional changes).
  - Recommend approval to the AO after minor changes to be reviewed by the Chair or designated IRB reviewer.
  - Defer pending substantive changes or additional information to be reviewed by the convened Committee.
  - Recommend disapproval

### 6.7.5 Amendment Disapproval

In the event that the convened IRB finds one or more of the line items of an amendment request submission unacceptable, the entire amendment will be disapproved. The PI will be notified of the disapproval via IRBNet. The Disapproval Memorandum will include a brief justification that identifies which line item(s) was not acceptable and why. The PI can resubmit a new amendment that

- Corrects the issues described in the Disapproval Memorandum;
- Provides additional justification to support the original request; or
- Includes all line items that the IRB found acceptable, less the line items that the IRB specifically disapproved.

**Revised Amendments Submitted after the IRB Disapproved the Previous Amendment Action**

The revised amendment will be treated as a new amendment request submission and, therefore, must include all appropriate documentation and a new version date. To streamline the review process, the DDEAMC IRB requires the PI to briefly describe how the original amendment was revised. Although the revised amendment will be treated as a new document, the IRB will attempt to minimize unnecessary duplicative reviews whenever possible.

On occasion, the IRB may contact an investigator or their designee to clarify or correct a minor issue or discrepancy rather than sending a formal Disapproval Letter. In this case, a new complete amendment request submission is not required. The PI shall make the change and resubmit the corrected protocol with all required documentation. A new Version Date must be inserted on the protocol title page and footer by the PI or designee when changes are made.

### 6.7.6 Principal Investigator Responsibilities after Approval of the Amendment

- Maintain copies of the amendment and all reviews and approvals maintained in IRBNet.
- Inform all associate investigators and key study personnel of the changes, and ensure revised procedures are followed.
- Promptly notify the IRB in writing of any change in a protocol's status.

**Re-consent/Notification of Subjects**

Modifications to the consent process must take into account both prospective research subjects and, if applicable, research subjects already enrolled in the study. The DDEAMC IRB will render a determination of whether the changes to the research activities require a change in the consent forms and, therefore, warrant re-consenting currently enrolled subjects or potentially notifying subjects who have completed research testing or interventions. Currently enrolled subjects who may be affected by the amendment will sign an addendum to the initial consent document or, less preferably, the modified consent form.

### 6.7.7 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"

15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #8: Continuing Review

### 6.8.1 Purpose

The purpose of this policy is to provide guidance on the federal regulations for continuing review and the procedure for timely completion of that requirement as part of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.8.2 Background

It is the policy of the DDEAMC IRB that research activities be periodically reviewed as continuing review at intervals appropriate to the degree of risk, but not less often than once per year.

### 6.8.3 Continuing Review

Continuing review and DDEAMC IRB recommendation for re-approval of research must occur on or before the date when DDEAMC IRB approval expires. The date by which a protocol must receive its continuing review is listed on the implementation approval memorandum. Review of a protocol amendment does not alter the date by which continuing review must occur. This is because continuing review is a review of the complete protocol, not simply any changes to it.

Continuing review is a substantive and meaningful process used to:

- Monitor an approved protocol.
- Determine if the study continues to satisfy the criteria set forth in 32 CFR 219.111 required for DDEAMC IRB approval of research.
- Determine if the anticipated risks and benefits are reflected in the actual experience of subjects.
- Determine that safeguards in place at the time of initial approval are, in fact, adequate to ensure the safety of subjects.
- Ensure that the study reflects any changes that have been made in the regulations for human subjects research since the last approval.

Based on the results of this process, the DDEAMC IRB maintains compliance with 32 CFR 219.109(a) and 219.113, 45 CFR 46.109 and 21 CFR 56.109, as applicable, and has the authority or responsibility to:

- Renew,
- Restrict,
- Require modifications, or
- Terminate a research project.

## Criteria for Determining Continuing Review Frequency at Initial Review

The DDEAMC IRB will decide the frequency of continuing review for each research protocol necessary to ensure the continued protection of the rights and welfare of research subjects [ 45 CFR 46.109(e) and 32 CFR 219(e)] at the time of the original approval and upon each subsequent approval for an additional time period. Continuing Review may be required more frequent than annually depending on the risks to subjects. Factors for making the decision about the frequency of review include the level of risk, location of the study, and any other factors that might affect the welfare of the subjects.

## DDEAMC IRB Authority

The DDEAMC IRB has the authority as granted by the Commander to:

- Modify the continuing review interval or request changes to the research if the risk/benefit ratio changes at any time during the study or
- Require additional information at any time, or
- Request an audit of the research to assure compliance by the research team and the safety of subjects.

## Continuing Review Determinations and Criteria

The DDEAMC IRB will use items based on the criteria in the Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP) Guidance on IRB Continuing Review of Research Draft 10/20/09 noted below in determining if:

1. A study requires continuing review on a more frequent basis than annually and
2. To assist in determining the frequency of the reviews

The criteria provide direction on the IRB member review of the complete study including the management of the research team and events that occur over the course of the study:

a. Nature of any risks posed by the research project;
    - Level of risks
    - Type of risks
    - Probability of risks (What is the likelihood of a severe adverse event?)
    - Magnitude of risks (What is the severity of the potential risks involved in this study?)
    - Degree of uncertainty regarding risks involved in the study;
    - Risk/Benefit ratio;
b. Subject population such as issues that relate to vulnerability;
c. Novel therapy or interventions;
d. Projected rate of enrollment;
e. Location of the study;
f. Factors related to the DDEAMC IRB experience with the PI and research team members:
    - Experience level in area being studied (Clinical Experience if applicable)
    - Experience as an investigator
    - Research and regulatory compliance history
    - IRB previous history with investigator

In addition to specifying a time interval, the DDEAMC IRB may also specify a subject enrollment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the IRB might require that continuing review occur either in six (6) months or after five (5) subjects have enrolled, whichever occurs first (OHRP Guidance on IRB Continuing Review of Research Draft 10/20/09).

**Establishing the Continuing Review Date for Protocols Reviewed at the Convened Meeting**

The continuing review period starts on the date of the convened IRB meeting at which the IRB reviewed and recommended approval of the research. Principal Investigators (PIs) are notified of the date by which the protocol must be renewed again via IRBNet when an original protocol or approval for an additional time period application is approved.

The DDEAMC IRB approval will expire on the day before the one year anniversary date of the convened meeting at which the IRB recommended approval if the IRB determines that the research must be renewed no sooner than one year. This date remains the valid research protocol expiration date even though the research activity may not have received IRB approval for implementation until a period of time after the IRB recommended approval. This may also result in a study approval period of less than one year. For example, a research protocol may be reviewed at the August 12th meeting but the investigator may not supply their response to the IRB required changes until October 1st. The changes are allowed to be made via the expedited procedure and the IRB Chair approves the changes effective October 10th. The approval date will be October 10th and the protocol approval expiration date will be August 11th for an approval period of less than one year.

When continuing review occurs annually and the IRB performs continuing review within 30 days before the research approval period expires, the IRB may retain the anniversary date as the date by which the next continuing review must occur.

The IRB must conduct Continuing Reviews at convened meetings at which a majority of the members of the IRB are present including at least one member whose primary concerns are in nonscientific areas [32 CFR 219.108(b)] except when an expedited review procedure is used.

**Establishing the Continuing Review Date for Protocols Reviewed Under the Expedited Review Categories**

The HHS human subjects regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364-60367 (see http://www.hhs.gov/ohrp/humansubjects/guidance/63fr60364.htm), and to the review of minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

The DDEAMC IRB is permitted to use expedited review for the continuing review of research that involves solely one or more of the activities published at 63 FR 60364-60367.

For a study approved under expedited review, approval for an additional time period must occur within one year of the date the DDEAMC IRB Chair or IRB member designated by the Chair (i.e., expedited reviewer) gives final recommendation for approval.

## Principal Investigator (PI) Timeframes and Responsibilities

In preparation for the Continuing Review, PIs are required to submit a Continuing Review Report and any required or requested relevant documents to the IRB prior to the expiration of the study. The report should be filed *at least* 45 days before the study approval period ends. The PI must use the DDEAMC's IRB DMRN Continuing Review Cover Sheet in IRBNet.

It is essential that the PI submit an accurate and complete Continuing Review Report and other required documents by the due date set by the DCI's Research Regulatory Compliance Office (RRCO) since the DDEAMC IRB does not have the authority to extend the approval period beyond the expiration date. It is the responsibility of the PI to ensure that continuing review is completed and approval for an additional time period is approved by the IRB prior to the expiration date.

It is recommended that the PI or designated research team member establish a method to track expiration dates to ensure that the protocol does not lapse. Some examples of tracking methods are the use of electronic calendars with reminders or spreadsheets to maintain multiple studies.

The PI should use this opportunity to provide information to the IRB about the study from the time of initial approval to the current time. For example, if the protocol was to enroll 100 subjects with two interventions but only 50 of those subjects were able to complete both interventions, then the IRB should be notified that 50 subjects were dropped/withdrawn and why (e.g., deployment, etc.)

## RRCO Preparation Timeframes and Responsibilities

To assist the PI in the request for continuing review process, RRCO staff will do the following as a courtesy:

- IRBNet sends an automated email 60 days prior to project expiration date with a copy to the individuals who have full access to the project.
- In addition to IRBNet notification to the PI, RRCO will attempt to contact the PI via phone or in person to ensure notification of the project's expiration date and the need to submit the continuing review. However, it is the responsibility of the PI to seek continuing review prior to the approval expiration.
- Confirm that the PI submitted a complete and accurate Continuing Review Report and all required documents by the due date set by the RRCO.
- The staff of the DCI's RRCO will verify that the required human research protections' training is current for all investigators and key research personnel.
- The RRCO will forward the complete research protocol package to the HPA or designee who will assign:
  - A primary reviewer for protocols that require convened committee review
  - A designated expedited reviewer for protocols that qualify for expedited review.
- The IRB is notified of continuing reviews as follows:
  - Protocols that require convened committee review will be placed on the next scheduled meeting agenda where it will be presented and reviewed
  - The protocols that qualify for expedited review will be placed on the agenda for notification to the convened IRB.

**Exempt Studies do not Require Continuing Review**

Exempt studies do not require annual continuing reviews. Unless otherwise specified, exempt protocols are considered as active for a one-year period.

### 6.8.4 Continuing Review Materials

The DDEAMC IRB must have the information required to conduct a substantive and meaningful review of the study in order to determine the status of the study. The documents and information that the IRB will consider are listed in the next section.

**Continuing Review Documentation and Information for IRB Member Review**

All DDEAMC IRB members shall have access to IRBNet which allows the member to review the protocol summary and status report on the progress of the research. The continuing review report shall include the following:

- Current protocol
- The number of individuals consented and enrolled (with gender breakdown) since initial IRB review and the last continuing review, as applicable.
- A summary of unanticipated problems, adverse events, deviations, and available information regarding adverse events and deviations
- Summary of any withdrawal of subjects since last review
- Summary of any complaints about the research
- Summary of any recent literature relevant to the research
- Summary of any amendments or modifications since the last review
- Any relevant multi-center reports
- Copy of current Informed Consent Form (ICF) and any newly proposed ICF
- Any relevant information, especially about risks
- A summary of interim findings and recent literature that may be relevant to the research
- A summary of amendments to the research since the last IRB review
- For FDA regulated research, the Investigator's Brochure, if available, including any modifications and ;
- Any other significant information and documents such as reports from DSMB or DSMC as available.

**Informed Consent Form (ICF), Currently Approved and Newly Proposed**

Each DDEAMC IRB member shall review the currently approved ICF and any newly proposed ICF. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in an updated ICF. The primary reviewer will verify that the copy of the IRB-stamped approved ICF submitted with the continuing review report is truly the correct approved version.

**Current Approved Protocol (including any Amendments since Initial Review)**

All DDEAMC IRB members, via IRBNet, have access to the most recent IRB approved protocol that contains any modifications previously approved by the Committee. The Primary Reviewer will have available, for review as needed, the complete IRBNet file including the, relevant IRB

meeting minutes, and any additional documents submitted by the PI with the Continuing Review Report. This access will be made available to all IRB members prior to and during the convened IRB meeting. This will allow members to resolve any questions that may arise during IRB deliberations on the study.

### 6.8.5 Responsibilities for Continuing Review Criteria for IRB Members and RRCO

The approval criteria for continuing review of ongoing IRB approved research protocols are the same as those established in 32 CFR 219.111 for the IRB approval of research used for the initial review. Therefore, it is the responsibility of the DDEAMC IRB members regardless of whether the protocol was originally approved via the convened committee or the expedited procedure to determine the following:

- Risks to subjects continue to be minimized and reasonable in relation to the anticipated benefits;
- Selection of subjects continues to be equitable;
- Informed consent continues to be appropriately obtained and documented;
- There are adequate provisions for monitoring the data collected to ensure the safety of the subjects, when appropriate;
- Adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data are provided;
- Appropriate safeguards for vulnerable populations are provided.
- Risks to subjects have not changed based on the review of new literature findings.

### 6.8.6 Convened IRB Continuing Review

The continuing review is scheduled for a DDEAMC IRB meeting held within 30 days of the protocol expiration date for research requiring continuing review by the convened Committee. The DDEAMC IRB reviews continuing research at convened meetings at which a majority of members are present, including at least one member whose primary concerns are in a nonscientific area.

**HPA or Designee Responsibilities**

A designated DDEAMC IRB member serves as primary reviewer (where possible the initial primary reviewer is used). If the initial primary reviewer is not available, the HPA or designee will review the continuing review submission to determine which member has the relevant expertise to conduct an in-depth evaluation of the research.

**Primary Reviewer System for Convened Review**

The DDEAMC IRB uses a modified primary reviewer system for actions requiring review by the convened DDEAMC IRB. This “modified” system provides that all IRB members, not just the primary reviewer, receive electronic copies via IRBNet of all convened board submissions, including all documents submitted by the PI rather than only a protocol summary and consent form. Primary reviewers are assigned protocols by the HPA or designee with consideration of their expertise or interest in the subject area, equal distribution of assignments, and availability to accept the task.

**Primary Reviewer Responsibilities**

The assigned primary reviewer should:

1. Evaluate the protocol to determine whether they have the expertise required to review the protocol. If the primary reviewer does not have the appropriate expertise, they must contact the HPA or designee as soon as possible so that a new primary reviewer or consultant with appropriate expertise can be assigned.
2. The primary or designated reviewer must not be involved in the conduct of the proposed research or have any other conflict of interest. If it is not obvious that a DDEAMC IRB member is, in fact, involved in a protocol (e.g., is not listed as a participating investigator), and the protocol is assigned to that member, it is that member's responsibility to inform the RRCO of this situation and to relinquish responsibility for reviewing the protocol.
3. The primary reviewer conducts an in-depth review of all materials in advance of the meeting using a reviewer checklist. The primary reviewer will present his or her findings at the convened IRB meeting. The reviewer will confirm that the requirements noted in Titel 32 CFR 219.111 are met.
4. The current continuing review report will be compared with the previous year's report to reveal any discrepancies, if applicable.
5. Contact the Investigator, when necessary, to request additional information and resolve outstanding issues using the IRBNet "Project Mail" in the submitted review package allowing for documented communication to become part of the IRB protocol file. This should be completed prior to the meeting date if this is part of a convened review.
6. Lead the discussion of the assigned research protocol.

**RRCO Responsibilities for Convened Committee Review**

1. The copy of the most recent informed consent form will be reviewed to determine if it was the appropriate version and if it was used within the correct approval dates indicated by the IRB approval stamp. The informed consent form(s) submitted for use during the next approval period should be compared with the version last approved by the IRB to determine if the correct version of the consent form has been provided.
2. For research requiring continuing review by the convened committee, the review is scheduled for an IRB meeting to be held within 30 days of the protocol's expiration date. If the study is due to expire, the RRCO staff will make every attempt possible to schedule the continuing review for the next available committee meeting.
3. The RRCO staff places the study on a meeting agenda. Information is available to the Committee members one week prior to the IRB meeting.
4. The RRCO staff "share" review materials with all members by sharing the Continuing Review Package submitted via IRBNet. IRBNet also allows members access to all documents submitted to the DDEAMC IRB in previous IRBNet packages using the project history. Materials "shared" with members include at a minimum:
    a. Approved protocol
    b. Currently approved consent form
    c. Recruitment documents
    d. Continuing Review Report Form
    e. Amendment requests approved within the current approval period

f. Any problem or adverse event reports

5. The RRCO staff will ensure that all IRB members have access to the complete IRB protocol file and relevant IRB minutes via IRBNet prior to and during the convened IRB meeting.
6. Minutes of DDEAMC IRB meetings document separate deliberation, actions, and votes for each protocol undergoing continuing review by the convened Committee. Any disputed issues will be recorded in the minutes.

**Non-Primary IRB Members Responsibilities at Convened Meetings**

1. All other IRB members review the provided materials prior to the meeting in enough depth to be familiar with them and be prepared to discuss the research at the meeting.
2. The Committee will discuss any problems identified by the primary reviewer or other members and will agree upon any necessary changes.

**Fully Convened IRB at Meeting**

Upon convened Committee review of the study, the convened committee may make one of the following determinations:

a. Recommend approval for an additional time period;
b. Recommend approval for an additional time period after minor modifications;
c. Defer due to the need for major changes or additional information or lack of time for adequate review; **or**
d. Request the Investigator place the study on Administrative Hold.

The convened IRB makes a determination with a recorded vote.

### 6.8.7 Continuing Review via the Expedited Review Process

**HPA Responsibilities**

The HPA or designee will assign the designated reviewer and will ensure that no IRB member participates in the expedited review of research in which the member has a conflicting interest, except to provide information requested by the DDEAMC IRB Chair or his designated reviewer [32 CFR 219.107(e)].

**Designed Expedited Reviewer Responsibilities**

1. The designated expedited reviewer conducts the review on behalf of the convened Committee using the same criteria for approval for an additional time period.
2. The designated expedited reviewer conducts a detailed and in-depth review of all materials using a reviewer checklist.
3. Upon review of the study, the designated expedited reviewer may make one of the following determinations:

    a. Recommend approval for an additional time period;
    b. Recommend approval for an additional time period after specific modifications;
    c. Defer to the convened Committee; **or**
    d. Request the Investigator place the study on Administrative Hold.

4. The designated expedited reviewer will provide the specific category permitting the expedited review of the study so that it can be included in the IRB meeting minutes.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367.

Continuing review of research may be conducted using expedited procedures if the research met the criteria for initial expedited review; **and** all procedures continue to meet the expedited review Categories 1–7 noted in Chapter 6 Policy #5 Expedited Review; **and** the continuing research activities must pose no more than minimal risk to subjects (as assessed by the designated reviewer).

**Expedited Review Category (8):**
Under Category (8), an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB as follows:

**(a)** Where:
- i. The research is permanently closed to the enrollment of new subjects;
- ii. All subjects have completed all research-related interventions; and
- iii. The research remains active only for long-term follow-up of subjects; OR

(b) Where no subjects have been enrolled (*i.e., interpreted to mean that no subjects have ever been enrolled at a particular site*) and no additional risks have been identified (*i.e., interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.*);

(c) Where the remaining research activities are limited to data analysis.

Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8) (a), (b), or (c) are satisfied for that site.

**Expedited Review Category (9):**
Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The determination that "no additional risks have been identified" does not need to be made by the convened IRB.

**RRCO Staff Responsibilities**

1. Ensure that the continuing review package in IRBNet is "shared" with the designated reviewer for review of the following documentation and any other documents maintained in the protocol's IRBNet project history to include documents submitted in the package.
2. The convened IRB is informed of the expedited continuing review designated reviewer's findings and recommendations during the next convened IRB Meeting on the agenda and the minutes.

**Moving Research Previously Approved as Meeting Expedited Category(ies) to Convened Review**

It is also possible that research activities that previously qualified for expedited review in accordance with HHS regulations at 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review. This change in review level is prompted at the time of continuing review or amendment review. Expedited studies no longer meeting the criteria for the expedited process will be reviewed by the IRB at a convened meeting.

### 6.8.8 Post-Review Actions

**Documentation and Communication with Investigators**

Principal investigators (PI) are notified via IRBNet of the decision of the DDEAMC IRB and any requested changes. The DDEAMC IRB provides final recommendation for approval for an additional time period when all required changes have been made, reviewed, and confirmed. The approval for continuation memorandum indicates the type of review and the approval expiration date. Refer to Chapter 7 Documentation of Human Research Protection Activities.

**RRCO Staff Responsibilities Post-Review Actions**

1. Select the appropriate email template using IRBNet.
2. The study email is forwarded via IRBNet to the Chair or designated expedited reviewer for review and approval.
    a. If the study was recommended for approval for an additional time period, the RRCO staff drafts the approval memo and forwards it with the continuing review report to the AO for review and approval.
        (1) Once approved, the RRCO staff provides via IRBNet the approval to the PI along with a copy of the approved version of the informed consent form (ICF), stamped with the dates of approval and expiration.
        (2) Uploads all documents to the "Board Documents" section of the package.
    b. If the study was recommended for approval for an additional time period after modifications, the RRCO drafts an email to the PI requesting revisions and forwards it to the Chair or designated reviewer for review and submission to the PI via IRBNet.
        (1) If the recommendation was for approval for an additional time period after specific modifications, the email shall notify the Principal Investigator that the

revisions and/or clarifications shall be reviewed on an expedited basis by the IRB chair or designated reviewer.

c. If the study was recommended for deferred, the RRCO drafts an email to the PI requesting revisions and forwards it to the Chair or designated reviewer for review and submission to the PI via IRBNet.

   (1) The email explains that the study:

   - Was deferred,
   - The IRB has not recommended approval for the research to continue, and that if approval is not recommended prior to the date that prior IRB approval lapses, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects [32 CFR 219.109(a) and 45 CFR 46.109(a)]must be stopped on that expiration date and
   - The study may not be continued beyond the expiration date of the prior approval, and the suspension of the study will continue until the continuing review report is approved.

   (2) The PI response is pre-reviewed by the RRCO staff for completeness. If complete, the RRCO staff places the study on the next available agenda and informs the assigned reviewer and the Chair. If the original reviewer is unable to review the study or present it at the meeting, another reviewer will be assigned in accordance with IRB policies and procedures.

d. If the PI is asked to place the study on Administrative Hold, the RRCO staff composes the appropriate email for review by the Chair or designated expedited reviewer for review and approval. The IO must approve the email for this action.

**Limitation and Extensions of the Continuing Review Approval for an Additional Time Period**

Per U.S. Army Medical Research and Materiel Command (USAMRMC) policy, intramural research protocols involving human subjects will be closed five years from the date of initial approval unless a 12-month extension is granted by the IRB of record. The IRB will notify investigators at year four (4), or at least nine (9) months in advance, that protocols are approaching the five (5)-year anniversary. Investigators will provide the IRB Chair with either their plan to submit a replacement protocol within three months of notification, or to provide a final report and close the protocol per Chapter 6 Policy #8 Study Closure.

### 6.8.9 Lapse in IRB Approval

Federal regulations state that there is no grace period extending the conduct of the research beyond the expiration date of IRB approval. The current IRB approval expires automatically if:

- The PI fails to provide a completed continuing review or closure submission to the IRB or
- The IRB has not reviewed and recommended approval of a research study by the expiration date specified by the IRB.

If the current IRB approval expires then all research activities must stop such as:

- Research procedures,

- Recruitment,
- Enrollment,
- Interventions,
- Data collection, and
- Data analysis

**Exception to Lapsed IRB Approval**

The only exception is when the IRB finds it in the best interests of already enrolled subjects to continue participating in the research interventions or interactions. Continuing participation of already enrolled subjects in a study with a lapse in IRB approval may be appropriate when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects. The determination that it is in the best interests of already enrolled subjects to continue to participate in the research may be made initially by the PI, but the PI must seek confirmation that the IRB agrees with this determination as soon as possible and within 3 business days. This determination may be made for all enrolled subjects as a group or for each individual subject.

If the IRB or PI determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects [32 CFR 219.109(a) and 45 CFR 46.109(a).

**RRCO Responsibilities**

When an IRB approved study expires because the Continuing Review was not renewed prior to the protocol approval expiration date, RRCO will:

1. Promptly prepares an email for approval by the IRB Chair on the day of expiration informing the PI that the study no longer has IRB approval and that the research cannot be re-opened without a Continuing Review Packet submission via IRBNet and e-mail followed by a signed email notifying the investigator of the expiration. Such expiration of IRB approval does not need to be reported to the Army Human Research Protections Office as a suspension of IRB approval under DoD regulations.
2. Ensure that the email is copied to the Department Chief, the AO, and if the research received second-level review, the Deputy, USAMRMC Office of Research Protections to include AHRPPO and OHRPO.
3. Place notification of the lapse in research on the agenda and in the minutes for the next available IRB meeting. This official email will also be posted in IRBNet if it is not sent as a project mail in the system.

**PI Responsibilities When IRB Approval of an Ongoing Study Lapses**

When IRB approval of an ongoing research study lapses, the PI will complete the Continuing Review and submit it to the IRB for review and approval as soon as possible. The PI may resume research activities for the study once the Continuing Review is approved by the convened IRB. This level of review will be required for all research protocols that have a lapse in continuing review. Note that if the PI has submitted the review in a timely manner and the IRB fails to complete the review then this is not considered a PI responsibility and no punitive action shall be placed on the PI.

**IRB Responsibilities When IRB Approval of an Ongoing Study Lapses due to PI Failure to Respond**

The IRB will document why the lapse occurred and the steps that the IRB is taking to prevent any such lapse of approval of the study from occurring again.

### 6.8.10 Non-Compliance

**PI Non-Compliance with Lapsed IRB Approval**

If the investigator continues to conduct the research after the study has expired and has not notified the IRB of the benefit to subjects within three (3) days, this becomes an issue of non-compliance and will be processed as described in the DDEAMC HRPP Non-Compliance policy Chapter 14.

**IRB Responsibilities for Non-Compliance**

The IRB is required to report the incidence of non-compliance to the Army Human Research Protections Office and USAMRMC Office of Research Protections.

**IRB Suspension or Termination of Approved Research at Continuing Review**

The IRB has the authority to suspend or terminate approval of ongoing research that is not being conducted in accordance with the IRB's requirements or that is associated with unexpected serious harm to subjects (32 CFR 219.113). A suspension or termination of IRB approval of research may occur anytime during the period for which IRB approval has already been given for the study.

Suspension of IRB approval may be appropriate when a significant issue is first identified and while the IRB investigates the matter. For example, if there is an allegation of serious noncompliance by an investigator, the IRB may suspend its approval of the research while the allegation is being investigated. In addition, the IRB will consider whether it is appropriate to notify subjects about the suspension and the reasons for it, and if so, when subjects should be notified, given that complete information may not be available.

The suspension or termination report from the IRB must include the reasons for the IRB's action (32 CFR 219.113) and the following information:

- The name of the institution conducting the research;
- The title of the research study and the title of any related grant, contract, or cooperative agreement;
- The name of the Principal Investigator (PI) for the study
- The number of the research study assigned by the IRB and the number of applicable awards
- A detailed description of the reason for the suspension or termination; and
- The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc).

**IRB Responsibility for Establishing Procedures for Continuing Beneficial Treatment During a Suspended or Terminated Approval Period**

When the IRB suspends or terminates its approval during the period for which IRB approval had already been given or disapproves a research project at the time of continuing review, the IRB will establish procedures to:

- Ensure that the rights and welfare of currently enrolled subjects are protected,
- Subjects are not put at risk, and
- Subjects receive appropriate care, if indicated, during the period of suspension or following the cessation of research.

This is particularly important with clinical trial studies. Continuation of subjects on interventions that were being administered under the research project may be appropriate on a temporary basis if the interventions hold the prospect of direct benefit to the subjects or if withholding the interventions poses increased risk to the subjects. If the IRB decides that already enrolled subjects will continue to receive the interventions that were being administered as a part of the research, data collection (especially safety information) will also be continued for the subjects.

**RRCO Reporting Responsibilities**

Suspension or termination of IRB approval will be promptly reported to the:

- PI
- Careline/Department Chief
- Program Directors for trainees
- Deputy Commander for Clinical Services (DCCS) as the Approving Official (AO)
- Commander as the Institutional Official (IO)
- Office of Research Protections (ORP) at MRMC, and
- Army Human Research Protections Office (AHRPO) [32 CFR 219.103(b)(5) and 219.113].

### 6.8.11 Identifying When Continuing Review is No Longer Required

Continuing review and re-approval of an IRB approved ongoing research study is required as long as the study continues to involve human subjects. DDEAMC IRB considers a research study to continue to involve human subjects as long as the investigators continue to obtain:

- Data about the subjects through intervention or interaction with them; or
- Private identifiable information (PII) about the subjects to include using, studying, or analyzing PII even if the information was already in the possession of the investigator before the research was initiated by the investigator.

A research project no longer involves human subjects once the investigator has finished obtaining data through interaction or intervention with subjects or obtaining PII on subjects, which includes the use, study, or analysis of de-identified PII so that individual subjects cannot be identified. Once all such activities described in the IRB –approved protocol are finished, the research project is no longer required to undergo continuing review but a final report must be submitted. Refer to Chapter 6 Policy #9 Study Closure.

### 6.8.12 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in Title 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. Title 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #9: Study Closure

### 6.9.1 Purpose

The purpose of this policy is to provide information about the resources that form the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.9.2 Background

The IRB needs to have the most current information to ensure that research risks and benefits are evenly distributed. Each project must report their findings.

### 6.9.3 Study Closure

It is the policy of the DDEAMC IRB that a final closure report must be filed by the Principal Investigator (PI) or designee at the completion of every research protocol submitted to the DDEAMC IRB. This includes projects that met the criteria for expedited and convened review. A closure report is a vital piece of the research process and is used to provide pertinent information to the IRB in its evaluation and approval of related studies. It is also provides an administrative notice for the Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO) to close its files.

1. A study may be closed if **all** of the following criteria are met:
    a. The study is closed to enrollment.
    b. All data collection is complete.
    c. All assays specified in the protocol have been performed.
    d. All data analyses identified in the protocol have been completed.
    e. All protocol objectives have been addressed.
    f. No subjects are still being followed for study related injury or illness.
    g. All obligations to the research participants have been fulfilled (e.g., promises to provide them with results of tests or overall study findings).
    h. No further analyses of identifiable (i.e., coded) data will be conducted. (Analyses of de-identified data may continue after study closure.)
2. Investigators need not wait for the end of the study approval period to submit a report. The Closure Report should be submitted to the RRCO by the PI no later than 30 days before the expiration of approval date.
3. If a study expires prior to the PI submitting a closure report or continuing review report, the PI must file a closure report within 30 days after receipt of notification that the protocol expired. Final reports submitted for a study that has expired for lapse in DDEAMC IRB

approval must include a description of activities that have occurred in the study since approval at the prior continuing review.

4. If a closure report or request for continuing review request has not been submitted within 30 days after expiration, the IRB will not review any NEW protocols from the PI until this reporting obligation is met.
5. Final reports may be reviewed and approved by an administrative process. This expedited review may be conducted by the HPA, IRB Chair or designated IRB member. In this circumstance, the reviewer may approve the final report and close the study or, if appropriate, he or she may defer a decision and refer the final report to the convened IRB.
6. If the PI of an active protocol is leaving the organization, note that the data belongs to the Careline, not the PI and at least 45 days prior to the estimated departure date the PI will do either of the following:
   a. Transfer the research to another investigator designated by the Department Chief, with sufficient expertise and experience in a relevant research area via an amendment to the protocol, which is reviewed and approved by the DDEAMC IRB; **or**
   b. Submit a Closure Report to the IRB.
7. If the PI leaves the organization without designating a successor PI or closing the protocol, unless the IRB-approved protocol designated an Acting PI available to oversee the study, all research activity shall be suspended. The PI's Careline/Department Chief is responsible for:
   a. Appointing a qualified PI and
   b. Taking steps to have the study reviewed and
   c. May have the records audited to maintain approval.

   If the DDEAMC IRB does not receive a Continuing Review Report or Closure Report within 45 days of the departure of the PI, the IRB will administratively close the protocol and provide written notification of this action as well as include this documentation in the IRBNet system.

   A study may also be administratively closed by the DDEAMC IRB without a closure report from the PI if the PI (or the Careline/Department Chief, in the case where a PI is unavailable) provides a written memo to the IRB affirming that the study was never initiated after IRB approval and that no subjects were ever enrolled in the study. The DDEAMC IRB will provide notification of this action as well as include this document in the IRBNet system.
8. The PI is responsible for ensuring that the data destruction plan in the protocol as approved by the IRB is completed.

### 6.9.4 Submission Requirements

The PI is responsible for submitting a completed Closure Report (Human Use Protocol) via the IRBNet system.

### 6.9.5 Re-approval of a Closed Protocol

The IRB recognizes that PIs may inadvertently close a protocol that should have remained in an active, approved status. If this occurs, the PI must contact the HPA for guidance and will often be asked to submit a new protocol to initiate review as regulations and guidance changes over time.

### 6.9.6 Deadlines

All deadlines are noted in Chapter 6, Policy #8 Deadlines for Submission by the PI to the IRB.

### 6.9.7 Exempt Studies - Closure of Protocols

The DDEAMC IRB requires the PI to submit a brief final report to DCI RRCO at the completion of the study. This report may be in the form of an abstract, journal manuscript, or one-page summary.

Once each year the RRCO staff will send the PI an email request for status of an exempt protocol. The PI will reply whether the study is currently active or has been terminated.

1. If the PI indicates the study is active, the email is filed in the protocol file.

2. If the PI indicates the study has been close, the email is filed in the protocol file, the file is marked closed. RRCO staff will change the status of the protocol in IRBNet as closed.

### 6.9.8 PI Responsibilities after Study Closure

Investigators may retain the research data collected, including identifiable private data, if consistent with the IRB-approved protocol and the Careline/Department/Service Chief approval (in writing and documented in IRBNet). Investigators must continue to honor any confidentiality protections.

Investigators or their Carelines (due to PCS, ETC, etc.) must retain research records pertaining to a closed research protocol for a minimum of fifty (50) years after the protocol closure date. Please refer to Chapter 7 Documentation of Human Research Protection Activities for document storage requirements.

1. Investigators must honor any other commitments that were agreed to as part of the approved research; for example, providing information about the study results to research subjects, or honoring commitments to compensate research participants for their participation.
2. Additionally, if investigators become aware of risks to subjects from their participation in the research for which the subjects have not been informed, the investigators must notify the IRB via the submission of an Adverse Event/Unanticipated Problem Report.

### 6.9.9 Process Overview

The PI prepares and submits the Study Closure Report once the PI has determined that all human research subject activities have ceased. The Study Closure Report includes the total number of subjects enrolled, tested, and withdrawn; a compilation of adverse events, problems, and amendments; and a summary of the findings. A manuscript may be substituted for the summary of the findings.

1. RRCO staff review all reports of study completion and, if needed, request further information from the PI to obtain missing elements, or to clarify any questions that may arise.

2. The HPA reviews the Closure Report and other documents submitted with the report. If no problems or discrepancies are found, the designated reviewer completes the process in IRBNet. If problems are found, they must be resolved before the protocol can be closed.

3. If the designated reviewer finds that the study does not qualify for closure, he or she will inform RRCO to contact the PI to instruct the investigator to submit the required corrections via IRBNet.

4. Upon DCI acceptance of the closure, RRCO changes the study status in IRBNet of the Protocol Tracking Log and updates the next IRB meeting agenda to report the study closure.

5. The protocol file is updated in IRBNet to reflect the status change and effective date.

### 6.9.10 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures

14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #10: Deadlines for Submission by the PI to the IRB

### 6.10.1 Purpose

The purpose of this policy is to provide deadlines to ensure compliance with the prompt reporting requirements in the federal regulations (32 CFR 219, 45 CFR 46 and 21 CFR 56) and complete packages are submitted to the DDEAMC IRB as an integral part of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.10.2 Background

Investigators and other research team members should be advised of deadlines for submission to the IRB. This knowledge will assist both the investigator and the IRB in planning.

**Submission Deadlines**

| Submission Type | Submission Deadline |
|---|---|
| New Protocol, Convened Review | A complete protocol packet must be submitted via IRBNet no later than the fifteenth ($15^{th}$) of the month prior to the month of the convened meeting to be considered for review at that meeting. |
| New Protocol, Expedited Review | N/A |
| New Protocol, Exempt Review | N/A |
| New Protocol, Emergency Use | N/A |
| New Protocol, Request for Research Determination | N/A |
| Responses to Required Revisions for New Protocols | Sixty days from the date of the DDEAMC IRB notification requiring changes. Protocols will be administratively withdrawn. |
| Amendment Request, Convened Review | Three weeks prior to convened meeting |

| | |
|---|---|
| Amendment Request, Expedited Review | N/A |

| Submission Type | Submission Deadline |
|---|---|
| Responses to Required Revisions for Amendments | Thirty days from the date of the DDEAMC IRB notification requiring changes. Protocols will be administratively withdrawn. |
| Annual Report for Exempt | Within one year of initial approval |
| Continuing Review, Convened | The 15th of the month prior to the date that the protocol approval expires. |
| Continuing Review, Expedited | The 15th of the month prior to the date that the protocol approval expires. |
| Responses to Required Revisions for Continuing Review | Thirty days from the date of the DDEAMC IRB notification requiring changes. All research activities must cease. |
| Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) | 24 hours followed by written report within one (1) week |
| Major Protocol Deviations | Initial: Within one (1) week<br>Follow-up: Summarize in the continuing review and closure report. |
| Minor Protocol Deviations | Initial: At the time of continuing review<br>Follow-up: Summarize in the continuing review and closure report. |
| Minor due to participant's non-adherence | At time of continuing review |
| Adverse Events, Unexpected and Related, Non-serious | Initial: Within one (1) week<br>Follow-up: Summarize unexpected and related (possibly related) expected adverse events in the continuing review and closure report. |

| Submission Type | Submission Deadline |
|---|---|
| Serious Adverse Events Related to Study Participation including Deaths | Initial: Phone or email as soon as becoming aware of the event, but in no case no more than one (1) week, even if all the information is not known to the DDEAMC IRB.<br><br>Follow-up: No more than one (1) month and upon completion of the event. |
| IND Safety Report | Accepted only if the sponsor provides a complete analysis of the event as an unanticipated problem involving risks to subjects or others including an analysis of the significance of the adverse event, with a discussion of previous similar events where appropriate. |

### 6.10.3 Working with the Deadlines

The DDEAMC IRB recommends the following methods to work within the deadlines:

1. Start early.
2. Review the appropriate policy before initiating the action.
3. Review the IRBNet standard operating procedures prior to submission especially those research team members who are infrequent users.

### 6.10.4 References

The following references are provided for informational purposes:

1. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2000.
2. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
3. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56, as applicable.

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #11: Response/Turnaround Times

### 6.11.1 Purpose

The purpose of this policy is to provide information about the amount of time estimated for protocol actions and review by the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

### 6.11.2 Background

Investigators and other research team members should be advised of realistic expectations about the turnaround times related to DDEAMC IRB submission types. This knowledge will assist both the investigator and the DDEAMC IRB in planning.

### 6.11.3 Information on Realistic Turnaround Times

Each protocol and subsequent actions requires administrative review by the DCI RRCO staff which is usually accomplished within one week of the receipt of action.

Expedited Procedures – New, Continuing Review, Amendments and Study Closures

Protocols and their actions that may be eligible for review via the expedited procedure as defined earlier in Chapter 6 usually require the following steps:

1. DCI RRCO conducts an administrative review and notifies the PI of any corrections that must be completed.
2. The PI makes the required corrections and notifies the DCI RRCO that revisions are complete.
3. The DCI RRCO confirms that all required corrections are complete.
    a. If complete, the HPA or designee or the IRB Chair/Vice-Chair assigns the protocol to an IRB member for review.
    b. If incomplete, the DCI RRCO returns the package to the PI for completion.
4. The IRB member conducts their review and notifies the DCI RRCO staff of any required changes.
5. DCI RRCO notifies the PI of any corrections that must be completed per the IRB member review of the protocol.
6. The PI makes the required corrections and notifies the DCI RRCO that revisions are complete.
7. The IRB member confirms that all required corrections are made and the protocol is approved via the expedited procedure.

If the protocol package is complete and the IRB questions are promptly responded to by the PI, then the review time from initial submission via IRBNet to IRB approval is approximately four weeks.

Convened Procedures – New, Continuing Review, and Amendments

1. The procedures are the same as the expedited procedure through step 6.
2. The IRB member confirms that all required corrections are made and the protocol is placed on the IRB Meeting Agenda for review by the convened committee.
3. The protocol is reviewed at the convened meeting and any changes required by the IRB are documented in the minutes.
4. The required changes are communicated to the PI.
5. The PI makes the required corrections and submits a "revision" package to the IRB.
6. The IRB member confirms that all required corrections are made and:
    a. The protocol may be recommended for approval to the IO via the Chair or Vice-Chair review.
    b. The protocol may be required to return to the convened IRB.
7. The Headquarters Level Administrative Review (HLAR) is conducted by CIRO.
8. The IO may approve the protocol upon the IRB Chair or designee recommendation.

If the protocol package is complete and the IRB questions are promptly responded to by the PI, then the review time from initial submission via IRBNet to IRB approval is approximately eight weeks. However, delays may occur at any stage in the process and extend the period.

### 6.11.4 Ways to Improve Turnaround Efficiency

There are two major components of a successful and prompt turnaround time for any action submitted to the IRB for review:

1. State of readiness and completion of the action
2. Communication between IRB staff and investigators

Suggestions from the IRB on improving the state of readiness and completion of the action are to review the appropriate chapter in the HRPP that correspond to the type of action. For example, if the investigator is submitting a new protocol for expedited review then Chapter 6 Policy #4 should be reviewed prior to the submission.

Users of IRBNet should take time to familiarize themselves with the system by utilizing available educational materials or consulting with RRCO staff to arrange for personalized instruction. Learning and adapting to new research review and approval process as necessary in order to achieve ongoing performance improvement. Common mistakes in IRBNet submissions are listed below for reference but the user should refer to the available educational materials on the IRBNet site prior to submitting any research documents.

| Common Error | Time Delay | Corrective Action |
|---|---|---|
| Required signatures missing for complete research team members to include all associate investigators and Careline/Department Chiefs | The package must be returned to the research team to make this change which will result in at least a two day delay. | Confirm that all required signatures are complete as soon as possible and prior to submission to the DCI RRCO via IRBNet. |

| Common Error | Time Delay | Corrective Action |
|---|---|---|
| Research team does not revise version dates on amended protocol documents | The package must be returned to the research team to make this change which will result in at least a two day delay. | Include the revised version date on all documents as they are changed for version control and to ensure that the most current versions of documents such as informed consents and protocols are being used. |
| Submission of a new revision packet when the pending package should be unlocked for revisions | The package must be returned to the research team to make this change which will result in at least a two day delay. | Make revisions to previously submitted actions pending in accordance with RRCO staff guidance. |

# Chapter 6: Institutional Review Board Policies and Procedures

## Policy #12: HIPAA and the Privacy Board

### 6.12.1 Purpose

The purpose of this policy is to provide information about the requirements imposed upon research by the DoD Privacy Rule (also known as HIPAA) and the Privacy Board in the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC). For the purposes of this HRPP, the DDEAMC Institutional Review Board (IRB) serves as the Privacy Board for all of the military treatment facilities (MTFs) listed on the DDEAMC Assurances under the Department of Defense and the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP).

### 6.12.2 Background

In the course of conducting research, researchers may obtain, create, use, and/or disclose individually identifiable health information. Under the Privacy Rule, covered entities are permitted to use and disclose protected health information (PHI) for research with individual authorization, or without individual authorization under limited circumstances set forth in the Privacy Rule.

### 6.12.3 Definitions

**Access to Data:** Members of the workforce of the covered entity have access to data via their roles under treatment, payment or operations (TPO). Access to information is governed by the Privacy Act of 1974 and DOD 5400.11-R.

**Authorization:** Written documentation of the research participants' authorization for use/disclosure of information about them for research purposes. The written documentation requirements and responsibilities are further defined in section 6.12.4.5.

**Coded:** (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens. This definition is proved from the Department of Health and Human Services (DHHS) Office of Human Research Protections Guidance on Research Involving Coded Private Information or Biological Specimens, dated 16 October 2008 available at http://www.hhs.gov/ohrp/policy/cdebiol.html. It is only provided as guidance to researchers who are seeking to use coded private information or coded biological specimens in the course of their resource.

**Covered Entity:** A health plan or a healthcare provider (organization or individual) who transmits any health information in electronic form in connection with a transaction. IAW 6025.18, C3.2.3.1., each military treatment facility and dental treatment facility (sometimes collectively referred to as MTFs) is the designated covered entity for all institutional healthcare provided by the facility and for all other healthcare provided by providers assigned to, employed by, or otherwise providing services in or on behalf of the facility.

**Data Use Agreement:** Satisfactory assurance in writing between the covered entity and the researcher (may be an internal researcher) in which the investigator agrees not to re-identify subjects. The researcher makes representations that they are only requesting the minimum necessary.

**De-identified data:** Health information that does not identify an individual and there is no reasonable basis to believe that the information can be used to identify an individual is not individually identifiable health information per 6025.18, C8.1.2. In addition, the Privacy Rule at section 164.514 allows a covered entity to determine that health information is not individually identifiable using either:

1. Statistical verification as specified in the Privacy Rule or

2. By removing certain pieces of information from each record, as specified in the Privacy Rule, about the individual, relatives, employers, or household members of the individual and having no knowledge that the remaining information could be used alone or in combination with other information to identify the individual. Under the second method of de-identification, in general, unique identifying numbers, characteristics, or codes must be removed if the health information is to be considered to be de-identified unless permitted by the Privacy Rule as a re-identification code. All of the 18 identifiers listed in the "identifiers" definition must be removed to create a de-identified data.

The requirements for de-identified data are discussed further in section 6.12.4.4.

**Disclosure:** The release, transfer, provision of access to, or divulging in any other manner of protected health information outside the entity holding the information (e.g., releasing PHI to a researcher at an academic medical center).

**Health Information:** Any information, in any form or medium, that:

1. Is created or received by a healthcare provider, health plan, public health authority, employer, life insurer, or school or university; and
2. Relates to the past, present, or future physical or mental health or condition of an individual; the provision of healthcare to an individual; or the past, present, or future payment for the provision of healthcare to an individual.

**Identifiers:** Identifies listed below apply to the individual or of relatives, employers, or household members of the individual Even if these are removed, other identifiers may be present which, used alone or in combination with other information, could identify an individual who is a subject of the information and thus, this list is not exhaustive. The DoD 6025.18-R, C8.1.3.2 and the Privacy Rule lists 18 identifiers which are:

1. Names
2. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census:
3. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
4. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
5. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
6. Telephone numbers.
7. Fax numbers.
8. Electronic mail addresses.
9. Social security numbers.
10. Medical record numbers.
11. Health plan beneficiary numbers.
12. Account numbers.
13. Certificate or license numbers.
14. Vehicle identifiers and serial numbers, including license plate numbers.
15. Device identifiers and serial numbers.
16. Web Universal Resource Locators (URLs).
17. Internet Protocol (IP) address numbers.
18. Biometric identifiers, including finger and voice prints.
19. Full-face photographic images and any comparable images, and
20. Any other unique identifying number, characteristic, or code, except as permitted by assigning a code or other means of record identification to allow information de-identified under this section to be re-identified by the covered entity, if:

    Derivation. The code or other means of record identification is not derived from or related to information about the individual and is not otherwise capable of being translated so as to identify the individual; and

Security. The covered entity does not use or disclose the code or other means of record identification for any other purpose, and does not disclose the mechanism for re-identification.

**Individually Identifiable Health Information:** Information that is a subset of health information, including demographic information collected from an individual, and;

1. Is created or received by a healthcare provider, health plan or employer; and
2. Relates to the past, present, or future physical or mental health or condition of an individual; the provision of healthcare to an individual; or the past, present, or future payment for the provision of healthcare to an individual; and
    a. That identifies the individual; or
    b. With respect to which there is a reasonable basis to believe the information can be used to identify the individual

**Informed Consent, Research:** Process documented with either an informed consent document or form for a research subject to participate in a research project/program.

**Investigator:** A person involved in the execution of research; designated the Principle Investigator when assuming overall responsibility for the research.

**Informed Consent, Treatment:** Process documented with either an informed consent document or form for a patient to consent for treatment or a procedure.

**Limited Data Set:** A limited data set is protected health information that excludes specified direct identifiers of the individual or of relatives, employers, or household members of the individual (DoD 6025.18-R, C8.3.2):

1. Names.
2. Postal address information, other than town or city, State and zip code.
3. Telephone numbers.
4. Fax number.
5. Electronic mail addresses.
6. Social security numbers.
7. Medical record numbers.
8. Health plan beneficiary numbers.
9. Account numbers.
10. Certificate or license numbers.
11. Vehicle identifiers and serial numbers, including license plate numbers.
12. Device identifiers and serial numbers.
13. Web Universal Resource Locators (URLs).
14. Internet Protocol (IP) address numbers.
15. Biometric identifiers, including finger and voice prints.
16. Full-face photographic images and any comparable images.

**Obtaining:** Identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and
2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

This definition is proved from the Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP) Guidance on Research Involving Coded Private Information or Biological Specimens, dated 16 October 2008 available at http://www.hhs.gov/ohrp/policy/cdebiol.html. It is only provided as guidance to researchers who are seeking to use coded private information or coded biological specimens in the course of their resource.

**Personally identifiable information (PII):** Personal information is defined in DoDD 5400.11 as information about an individual that identifies, links, or is unique to, or describes him or her, e.g., a Social Security Number; age; military rank; civilian grade; marital status; race; salary; home/office phone numbers; other demographic, biometric, personnel, medical and financial information, etc. Such information is also known as personally identifiable information (e.g., information which can be used to distinguish or trace an individual's identity, such as their name, Social Security Number, date and place of birth, mother's maiden name, and biometric records, including any other personal information which is linked or linkable to a specified individual).

**Privacy Board:** DoD has authorized IRBs to serve as Privacy Boards for the purpose of reviewing and approving Waivers of Authorization IAW DoD 6026.18-R, C7.9. The required composition for a Privacy Board is established at DoD 6026.18-R, C7.9.1.1.1.

**Protected health information (PHI):** IAW DoD6026.18-R, DL1.1.28., individually identifiable health information that is a subset of health information, including demographic information collected from an individual, and:

1. Is created or received by a healthcare provider, health plan or employer; and
2. Relates to the past, present, or future physical or mental health or condition of an individual; the provision of healthcare to an individual; or the past, present, or future payment for the provision of healthcare to an individual; and
    a. That identifies the individuals; or

b. With respect to which there is a reasonable basis to believe the information can be used to identify the individual

**Psychotherapy Notes:** IAW DoD 6026.18-R, DL 1.1.29, these are notes recorded (in any medium) by a healthcare provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.

**Recruitment:** Process of identifying, contacting and informing individuals about a study for the purpose of enrolling subjects into the study.

**Research:** A systematic investigation, including research, development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

**Research Informed Consent Process:** The informed consent process involves three key features: (1) disclosing to potential research subjects information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. Informed consent must be legally effective and prospectively obtained. The documentation of the process is preferred on the DA Form 5303.

**Use:** IAW DoD 6026.18-R, DL1.1.38, with respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within an entity that maintains such information.

**Waiver of Authorization:** A waiver of authorization may occur in whole or in part. See section 6.12.4.6 for additional information.

**Workforce:** IAW DoD 6026.18-R, DL1.1.39, employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of such entity, whether or not they are paid by the covered entity.

### 6.12.4 Researchers and HIPAA Compliance

A covered entity may provide investigators access to protected health information (PHI) for research purposes through the following mechanisms:

1. Obtaining representations under the Preparatory to Research (PTR) Provision
2. Obtaining representations under the Research on Decedents (RD) Provision
3. Provision of a Limited Data Sets under a signed Data Use Agreement

4. Provision of de-identified data
5. Research Use/Disclosure with signed and valid Individual Authorization; or
    a. A signed Alteration of the Individual Authorization for Research Use/Disclosure as approved by the Privacy Board
    b. An Waiver of the Individual Authorization for Research Use/Disclosure as approved by the Privacy Board

### 6.12.4.1 Preparatory to Research Provision

The preparatory to research (PTR) provision permits covered entities to use or disclose protected health information for purposes preparatory to research. These types of activities may include such activities as to prepare a research protocol, including design, or assessing the feasibility of conducting a study, or as to aid study recruitment. However, the provision at 45 CFR 164.512(i)(1)(ii) does not permit the researcher to remove protected health information from the covered entity's site. As such, a researcher who is an employee or a member of the covered entity's workforce could use protected health information to contact prospective research subjects.

Activities that would be considered as PTR would be:

1. Developing the research questions
2. Determining the feasibility of the study such as determining the available number and eligibility of potential study subjects
3. Development of inclusion and exclusion criteria and
4. Recruitment

A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.

Recruitment

The preparatory research provision allows an internal researcher to identify prospective research participants for purposes of seeking their authorization to use or disclose protected health information for a research study. The PHI used to identify prospective research participants could include contact information, diagnosis or condition, and other information necessary to determine study eligibility. However, the actual process of the recruitment phase for research subjects is under research activities and requires prospective IRB approval.

Therefore, covered health care providers and patients may continue to discuss the option of enrolling in a clinical trial without patient authorization, and without an Institutional Review Board (IRB) or Privacy Board waiver of the authorization.

If the investigators/researchers are ***not*** members of the CE, they may not use the preparatory to research provision to contact prospective research subjects. Rather, the outside researcher could obtain contact information through a partial waiver of individual authorization by an IRB or

Privacy Board as permitted at DOD 6025.18-R, C7.9 and 45 CFR164.512(i)(1)(i). The IRB or Privacy Board waiver of authorization permits the partial waiver of authorization for the purposes of allowing a researcher to obtain protected health information as necessary to recruit potential research subjects. For example, even if an IRB does not waive informed consent and individual authorization for the study itself, it may waive such authorization to permit the disclosure of protected health information as necessary for the researcher to be able to contact and recruit individuals into the study.

**Investigator Responsibilities**

Investigators may be researchers who are part of the covered entity (individuals who may use PHI) or they may be external to the covered entity (PHI is disclosed to the researcher). Protocols may use both types of researchers on one project. The researchers should work with the IRB serving as the Privacy Board to ensure that PHI is protected.

Investigators have many responsibilities from the inception of the protocol to the long-term storage of research documents. These responsibilities are in addition to their routine duties. The investigator should prepare the research protocol to provide the required information for the IRB serving as the Privacy Board to ensure compliance with DOD 6025-18R. Use the following sections to guide protocol development.

Provide written representations from each investigator/researcher on the project via IRBNet that the use or disclosure of the protected health information is solely to:

1. Prepare a research protocol or for similar purposes preparatory to research
2. That the researcher will not remove any protected health information from the covered entity, and
3. Representation that protected health information for which access is sought is necessary for the research purpose.

Under these provisions, no PHI may be removed from the covered entity during the course of the review.

Provide a listing of individuals whose PHI is used to the HIPAA Privacy Officer, or designee, for purposes of an accounting of disclosures that occurred under the Preparatory to Research provision. Additional information that must be provided includes:

1. The date of the disclosure.
2. The name of the entity or person who received the protected health information.
3. A brief description of the protected health information disclosed.
4. A brief statement of the purpose of the disclosure that reasonably describes the basis for the disclosure.

**Research Regulatory Compliance Office (RRCO) Responsibilities**

1. The RRCO staff will review the written representation from the investigator/researcher to ensure that the required regulatory information is complete.
2. Prepare a letter of approval for this action and publish it via IRBNet.
3. Notify the HIPAA Privacy Officer or designee of the preparatory to research provision.

**HIPAA Privacy Officer Responsibilities**

Maintain the listing of individuals whose PHI was used under the PTR provision IAW DoD 6025.18-R, C14.10.

### 6.12.4.2 Research on PHI of Decedents

Using information derived from the medical records or samples from decedents does not meet the definition of research and would not require IRB approval. However, the Privacy Rule includes the use of decedent information and requires privacy board review.

**Investigator Responsibilities**

Submit a request to use decedent's information to the DCI via IRBNet for a determination of research not involving human subjects (see Chapter 6, Policy #3 for additional guidance).

**Research Regulatory Compliance Office (RRCO) Responsibilities**

The RRCO staff will review the project description to determine if the project meets the definitions of research and research involving human subjects (see Chapter 6, Policy #3 for additional information.)

Notify the HIPAA Privacy Officer or designee of determination.

**HIPAA Privacy Officer Responsibilities**

Maintain the listing of individuals whose PHI was used under the Research on Decedents provision IAW DoD 6025.18-R, C7.9.1.3.

**IRB Responsibilities**

There are no IRB responsibilities if the project only uses decedent information as this does not meet the regulatory definition of research (see Chapter 6, Policy #3 for additional information). However, the privacy board review requirement is still in effect.

### 6.12.4.3 Limited Data Set

Protected Health Information (PHI) may be disclosed to investigators/researchers with a Data Use Agreement (DUA) for a Limited Data Set (LDS). These may be internal or external investigators. Data use agreements are maintained by the HIPAA Privacy Officer or designee.

This agreement does not require an internal member of the workforce to serve in a research capacity as they are not using the data for research but supplying it to a researcher after it was collected for clinical or treatment purposes. The workforce member would not be considered as an investigator as they are not involved in conducting the research. DHHS OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. Note that if the individuals who provide coded information or specimens collaborate on other activities related to the conduct of this research with the investigators who receive such information or specimens, then OHRP would consider such additional activities to constitute involvement in the conduct of the research. Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research.

A data use agreement entered into by both the covered entity and the researcher, pursuant to which the covered entity may disclose a limited data set to the researcher for research, public health, or health care operations. See 45 CFR 164.514(e).

The data use agreement must:

- Establish the permitted uses and disclosures of the limited data set by the recipient, consistent with the purposes of the research, and which may not include any use or further disclosure by the recipient that would violate the Rule if done by the covered entity;
- Establish who is permitted to use or receive the data; and
- Require the recipient to agree to the following:
    - Not to use or disclose the information other than as permitted by the data use agreement or as otherwise required by law;
    - Use appropriate safeguards to prevent the use or disclosure of the information other than as provided for in the data use agreement;
    - Report to the covered entity any use or disclosure of the information not provided for by the data use agreement of which the recipient becomes aware;
    - Ensure that any agents, including a subcontractor, to whom the recipient provides the limited data set, agrees to the same restrictions and conditions that apply to the recipient with respect to the limited data set; and
    - Not to identify the information or contact the individual.

**Requestor's Responsibilities**

Requestors are responsible for submitting a data use agreement (DUA) to the Privacy Board of record. The DUA should be submitted with the project plan for routing to the HIPAA Privacy Officer or designee and the JAG representative. Requestor must work with PAD and other areas

of the covered entity prior to entering into a DUA to assure that this information can be obtained and provided.

If the activity meets the definition of research involving human subjects that is conducted or engaged in by someone who falls under the DDEAMC Assurance, a copy of the DUA must be submitted with the rest of the protocol submission to the IRB of record for DDEAMC. The LDS may not be released by DDEAMC without demonstration by the requestor of appropriate IRB approval.

If the activity meets the definition of research involving human subjects that is NOT conducted or engaged in by someone who falls under the DDEAMC Assurance, DDEAMC is supporting the research. The LDS may not be released by DDEAMC without demonstration by the requestor of appropriate IRB approval.

**Research Regulatory Compliance Office (RRCO) Responsibilities**

RRCO staff will review the submitted DUA to ensure it contains all required elements and forward to the HIPAA Privacy Officer or designee and JAG representative. The HIPAA privacy officer or designee will review the Data Use Agreement in conjunction with the JAG representative and will recommend approval of the DUA to the Commander or his designee prior to the information being released by the covered entity.

**HIPAA Privacy Officer Responsibilities**

1. Ensure that a limited data set is not released without a DUA signed by both the requestor/recipient and the covered entity, and when appropriate, IRB approval.
2. Maintain the executed data use agreements.

**IRB Responsibilities**

The IRB will not need to be involved with the review and approval of the DUA but must consider its implications as presented in the protocol during its review of criteria for IRB approval of research and specifically, a review of the criteria for Privacy and Confidentiality Protections. However, the privacy board review requirement is still in effect.

### 6.12.4.4 De-Identified Data

The Privacy Rule permits a covered entity to determine that health information is de-identified even if the health information has been assigned, and retains, a code or other means of record identification, provided that the code is not derived from or related to the information about the individual and could not be translated to identify the individual and the covered entity does not use or disclose the code for other purposes or disclose the mechanism for re-identification.

Under the HHS Protection of Human Subjects Regulations, if an investigator obtains private information about living individuals for research purposes and that private information retains a link to individually identifying information, such private information ordinarily would be considered by OHRP to be individually identifiable to the investigator and would qualify as research involving human subjects. However, OHRP does not ordinarily consider such information to be individually identifiable to the investigator if:

1. The investigator and the holder of the individually identifying information sign an agreement prohibiting the release of individually identifying information to the investigator under any circumstances, or
2. There are other legal requirements prohibiting the release of the link to the investigator.

**Investigator Responsibilities**

Investigators are responsible for submitting a project plan to the Privacy Board of record for their approval. This plan should include the agreement noted in item one above or provide the other legal requirements noted in number two. The investigator should also provide the data collection tool and follow the submission requirements noted in Chapter 6, Policy 4 Expedited Research.

**Research Regulatory Compliance Office (RRCO) Responsibilities**

The RRCO staff should follow the responsibilities in Chapter 6, Policy 4 Expedited Research**.**

**IRB Responsibilities**

The IRB should follow the responsibilities in Chapter 6, Policy 4 Expedited Research.

The IRB confirms that this project is using the minimum necessary to accomplish the intended purpose of the use, disclosure, or request. However, the privacy board review requirement is still in effect.

### 6.12.4.5 Research Use/Disclosure with Authorization

**Using Authorization Forms**

The Privacy Rule also permits covered entities to use or disclose protected health information for research purposes when a research subject/participant authorizes the use or disclosure of information about him or herself. Today, for example, a research participant's authorization will typically be sought for most clinical trials and some records research. The Privacy Rule has a general set of authorization requirements that apply to all uses and disclosures, including those for research purposes. However, several special provisions apply to research authorizations:

- Unlike other authorizations, an authorization for a research purpose may state that the authorization does not expire, that there is no expiration date or event, or that the authorization continues until the "end of the research study;" and
- An authorization for the use or disclosure of protected health information for research may be combined with a document for consent to participate in the research, or with any other legal permission related to the research study.

In this case, documentation of IRB or Privacy Board approval of a waiver of authorization is not required for the use or disclosure of protected health information. To use or disclose protected health information with authorization by the research participant, the covered entity must obtain an authorization that satisfies the requirements of 45 CFR 164.508. This method of obtaining written authorization for the use and disclosure of PHI from a subject is the most common method and allows the greatest flexibility for the research team. It is usually obtained in conjunction with the research informed consent process.

Protocols that are determined by the IRB to be no greater than minimal risk are eligible for a waiver (whole or partial) of authorization. If the IRB determines a project to be greater than minimal risk, the project is not eligible for a waiver (whole or partial).

A research subject may revoke his/her Authorization at any time. However, a covered entity may continue to use and disclose PHI that was obtained before the individual revoked Authorization to the extent that the entity has taken action in reliance on the Authorization. In cases where the research is conducted by the covered entity, this would permit the covered entity to continue using or disclosing the PHI as necessary to maintain the integrity of the research, as, for example, to account for a subject's withdrawal from the research study, to conduct investigations of scientific misconduct, or to report adverse events.

**Investigator Responsibilities**

The template DDEAMC HIPAA Authorization for Use and Disclosure of PHI is available in the IRBNet Forms and Templates Library for research team member's use. Investigators are responsible for submitting the DDEAMC HIPAA Authorization for Use and Disclosure of PHI to the Privacy Board of record for their approval. The Authorization must be written in plain language.

The Privacy Rule specifies core elements and required statements that must be included in an Authorization. An Authorization is not valid unless it contains all of the required elements and statements. An Authorization form may also, but is not required to, include additional, optional elements so long as they are not inconsistent with the required elements and statements and are not otherwise contrary to the Authorization requirements of the Privacy Rule. An Authorization, whether prepared by a covered entity or by a person requesting PHI from a covered entity, must include the following core elements and required statements:

## Authorization Core Elements

- Description of PHI to be used or disclosed (identifying the information in a specific and meaningful manner).
- The name(s) or other specific identification of person(s) or class of persons authorized to make the requested use or disclosure.
- The name(s) or other specific identification of the person(s) or class of persons who may use the PHI or to whom the covered entity may make the requested disclosure.
- Description of each purpose of the requested use or disclosure. Researchers should note that this element must be research study specific, not for future unspecified research.
- Authorization expiration date or event that relates to the individual or to the purpose of the use or disclosure (the terms "end of the research study" or "none" may be used for research, including for the creation and maintenance of a research database or repository).
- Signature of the individual and date. If the Authorization is signed by an individual's personal representative, a description of the representative's authority to act for the individual.

## Authorization Required Statements

- The individual's right to revoke his/her Authorization in writing and either:

    1. The exceptions to the right to revoke and a description of how the individual may revoke Authorization or
    2. Reference to the corresponding section(s) of the covered entity's Notice of Privacy Practices (NPP).

- Notice of the covered entity's ability or inability to condition treatment, payment, enrollment, or eligibility for benefits on the Authorization, including research-related treatment, and, if applicable, consequences of refusing to sign the Authorization.
- The potential for the PHI to be re-disclosed by the recipient and no longer protected by the Privacy Rule. This statement does not require an analysis of risk for re-disclosure but may be a general statement that the Privacy Rule may no longer protect health information.

Note: If the planned research will require the use of psychotherapy notes in addition to medical record, then two separate authorizations must be completed IAW DoD 6025.18-R. The term “psychotherapy notes” is specifically defined and used in the HIPAA Privacy Rule and DoD 6025.18-R: Psychotherapy notes means "(n)otes recorded (in any medium) by a healthcare provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or group, joint, or family counseling session and that are separated from the rest of the individual's medical record." This does NOT include notes regarding medication prescription and monitoring, counseling start and stop times, frequency and modalities of treatment, clinical test results, or any summary of the diagnosis,

functional status, treatment plan, symptoms, prognosis, and progress to date; these notes are not given the heightened protections of psychotherapy notes, but they do constitute protected health information (PHI) that is otherwise given minimum privacy protections under HIPAA. See, DoD 6025.18-R at DL1.1.29.

Sections C5.4 and C8.9 of DoD 6025.18-R require an authorization for drug and alcohol abuse program patient records comply with the special rules protecting the confidentiality as set forth in the Alcohol, Drug Abuse and Mental Health Administration Reorganization Act, 42 U.S.C 290dd-2 (ADAMHA) and implemented in 42 CFR Part 2. The requirements for a written consent for the disclosure of patient records from an alcohol and drug abuse program include the same elements as HIPAA, and HIPAA actually requires three additional elements that are not otherwise required within 42 CFR Part 2:

1. A statement about the CE's ability/inability to condition the authorization on treatment, payment, eligibility, or enrollment;
2. A statement that the PHI may no longer be protected by Federal HIPAA privacy law, and
3. For marketing, a statement when CE gets direct or indirect remuneration.

If the planned research will require the use of Alcohol and Drug Abuse Program patient records in addition to medical records, a compound authorization may be completed IAW DoD 6025.18-R. The description of the PHI to be used and disclosed must be specific to include an "entire medical record" or "complete patient file" as well as the specifically stating what personally identifiable information will be used/disclosed from the patient alcohol and drug patient record (in a way the patient understands that their alcohol and drug program patient records will be used in the research study).

Copies of the signed Authorization(s) must be provided to the subject or their authorized representative and the original must be maintained by the investigator for at least six years after the closure of the project.

**Research Regulatory Compliance Office (RRCO) Responsibilities**

Confirm that the Authorization is valid and follow the procedures for review under Chapter 6, Policy #5 Expedited Review or Chapter 6, Policy #6 Convened Board Review.

**IRB Responsibilities**

Confirm that the Authorization is valid and follow the procedures for review under Chapter 6, Policy #5 Expedited Review or Chapter 6, Policy #6 Convened Board Review.

### 6.12.4.6 Obtaining Alterations of Authorization or Waivers of Authorization

This provision of the Privacy Rule might be used, for example, to conduct records research, when researchers are unable to use de-identified information, and the research could not practicably be conducted if research participants' authorization were required. Protocols that are determined by the IRB to be no greater than minimal risk are eligible for an alteration or waiver (whole or partial) of authorization. If the IRB determines a project to be greater than minimal risk, the project is not eligible for alteration or waiver (whole or partial).

**Waiver of HIPAA Authorization**

A waiver in whole occurs when the IRB as the Privacy Board determines that no Authorization will be required for a covered entity to use or disclose PHI for a particular research project because certain criteria set forth in the Privacy Rule have been met (see section 164.512(i) of the Privacy Rule). For example, if a study involved the use of PHI pertaining to numerous individuals where contact information is unknown, and it would be impracticable to conduct the research if Authorization were required, an IRB could waive all of the Authorization requirements for research participants if the IRB determined that all of the Privacy Rule waiver criteria had been satisfied. If the IRB approves such a waiver, the receipt of the requisite documentation of the approval permits a covered entity to use or disclose PHI in connection with a particular research project without Authorization.

**Alteration of HIPAA Authorization**

An IRB may also approve a request that removes some, but not all, required elements of an Authorization (an alteration). For example, an IRB may alter the Authorization to remove the element that describes each purpose of the requested use or disclosure where, for example, the identification of the specific research study would affect the results of the study. Before a covered entity could use or disclose PHI pursuant to the altered Authorization, however, it must receive documentation that an IRB determined that all of the Privacy Rule waiver criteria at section 164.512(i)(2)(ii) had been satisfied. Any subsequent use or disclosure of PHI by a covered entity for a different research study would require an additional Authorization, except as permitted without Authorization under section 164.512(i) (e.g., with a waiver of Authorization) or 164.514(e) (i.e., as a limited data set with a data use agreement).

**Criteria for Approval of Alteration or Waiver**

The Privacy Rule establishes the criteria to be evaluated by an IRB in approving an Authorization waiver or alteration. Furthermore, the criteria for an IRB waiver or alteration of the Authorization are consistent with the criteria for IRB waiver of the informed consent requirements contained in the HHS Protection of Human Subjects Regulations. For a covered entity to use or disclose PHI under a waiver or an alteration of the Authorization requirement, it must receive documentation of, among other things, the IRB's determination that the following criteria have been met:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    - an adequate plan to protect the identifiers from improper use and disclosure;
    - an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
    - adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
2. The research could not practicably be conducted without the waiver or alteration; and
3. The research could not practicably be conducted without access to and use of the protected health information.

**Investigator Responsibilities**

The criteria for approval of Alteration or waiver of authorizations must be covered in the protocol templates completed by the researcher/investigator and must be satisfied for the DDEAMC IRB as the Privacy Board to approve an alteration or waiver of authorization under the Privacy Rule.

The investigator is also responsible for providing a listing of individuals whose PHI is used to the HIPAA Privacy Officer or designee for purposes of an accounting of disclosures that occurred under a waiver. This listing must include the additional requirements for identified in paragraph 6.12.4.1 for disclosures Preparatory to Research.

**Research Regulatory Compliance Office (RRCO) Responsibilities**

1. Confirm that the alteration or waiver of authorization is appropriate for the specific project:
    - Routine HIPAA Authorization
    - NOTE: If the patients' information needed is from either the Psychotherapy Notes or the Alcohol and Drug Abuse Program Patient Records, then a waiver is not appropriate.
2. Review the waiver request to determine if it is appropriate.
3. Forward to the appropriate board or member (designee or convened board) for action.
4. Prepare documentation based on the reviewer or board's decision, to ensure that the required regulatory documentation is captured.
5. Notify IRB of outcomes via the agenda and minutes.

**IRB Responsibilities**

Confirm that the project is no greater than minimal risk. Review requests to ensure documentation supports the need and meets regulatory criteria for approval.

**Documentation of Authorization Waiver or Alteration Determinations**

The DDEAMC IRB or designated reviewer provides the required documentation as noted below via their approval letter of all of the following:

- Identification of the DDEAMC IRB as the approving authority and the date on which the alteration or waiver of authorization was approved;
- A statement that the DDEAMC IRB has determined that the alteration or waiver of authorization, in whole or in part, satisfies the three criteria in the Rule;
- A brief description of the protected health information for which use or access has been determined to be necessary by the DDEAMC IRB;
- A statement that the alteration or waiver of authorization has been reviewed and approved under either normal or expedited review procedures; and
- The signature of the chair or other member, as designated by the chair, of DDEAMC IRB, as applicable.

### 6.12.5 IRB/Privacy Board Levels of Review

**Expedited Review**

The Privacy Rule allows the use of expedited review procedures to approve a waiver or alteration of the Authorization requirement. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity is on the HHS or FDA list of approved categories and involves no more than minimal risks. Protocols that are determined by the IRB to be no greater than minimal risk are eligible for a waiver (whole or partial) of authorization. If the IRB determines a project to be greater than minimal risk, the project is not eligible for a waiver (whole or partial).

In addition, 32 CRR 219.110, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research protocol, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, since this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB chair or by one or more experienced reviewers designated by the chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If the DDEAMC IRB uses expedited review procedures, it notifies the members via the IRB meeting agenda and minutes of the requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure. If the head of the Federal department or agency (or his/her designee) regulating the research has restricted, suspended,

terminated, or chosen not to authorize an institution or IRB to use expedited review procedures, the IRB cannot grant waivers or alterations of the Authorization requirement on an expedited basis.

**Convened Board Review**

The Privacy Rule also allows the use of convened board review procedures to approve a waiver or alteration of the Authorization requirement. A member with a conflicting interest may not participate in the review. Protocols that are determined by the IRB to be greater than minimal risk are not eligible for a waiver (whole or partial).

### 6.12.6 Accounting for Research Disclosures

In general, the Privacy Rule gives individuals the right to receive an accounting of certain disclosures of protected health information made by a covered entity. See 45 CFR 164.528. This accounting must include disclosures of protected health information that occurred during the six years prior to the individual's request for an accounting, or since the applicable compliance date (whichever is sooner), and must include specified information regarding each disclosure. A more general accounting is permitted for subsequent multiple disclosures to the same person or entity for a single purpose. See 45 CFR 164.528(b)(3). Among the types of disclosures that are exempt from this accounting requirement are:

- Research disclosures made pursuant to an individual's authorization;
- Disclosures of the limited data set to researchers with a data use agreement under 45 CFR 164.514(e).

In addition, for disclosures of protected health information for research purposes without the individual's authorization pursuant to 45 CFR164.512(i), and that involve at least 50 records, the Privacy Rule allows for a simplified accounting of such disclosures by covered entities. Under this simplified accounting provision, covered entities may provide individuals with a list of all protocols for which the patient's protected health information may have been disclosed under 45 CFR 164.512(i), as well as the researcher's name and contact information. Other requirements related to this simplified accounting provision are found in 45 CFR 164.528(b)(4).

**Investigator Responsibilities**

Provide a listing to the HIPAA Privacy Officer or designee an accounting of disclosures that occurred under:

1. Preparatory to Research
2. Waiver of HIPAA Authorization

**References:**

The following references are provided for informational purposes:

1. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
2. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
3. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E. 45 CFR 164.501, 164.508, 164.512(i) (See also 45 CFR 164.514(e), 164.528, 164.532)
4. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
5. Title 21 Code of Federal Regulations (CFR) Parts 50 and 56. Food and Drug Administration Regulations for the Protection of Human (as applicable).
6. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
7. Department of Defense Directive 5400.11-R: DoD Privacy Program, 1 September 2011
8. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
9. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
10. Title 5 U.S.C. 552a, Privacy Act of 1974.
11. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.
12. Health Information Privacy, accessed 20 December 2012, http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/research.html
13. Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP), *"Guidance on Research Involving Coded Private Information or Biological Specimens"*, dated 16 October 2008 available at http://www.hhs.gov/ohrp/policy/cdebiol.html.

# Chapter 7: Documentation of Human Research Protection Activities

## 7.1 Purpose

The purpose of this policy is to provide direction about the required documentation of human research protection (HRPP) activities at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 7.2 Background

Human Research Protection Program (HRPP) records will be maintained in full accordance with Department of Defense Instruction "Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research", (DoDI 3216.02) Department of the Army (DA) Records Control Schedule, Department of Defense (DoD) regulations at 32 CFR 219, and Food & Drug Administration (FDA) regulations (21 CFR 50 and 56), when applicable. The HRPP records will be treated as confidential documents. All records shall be accessible for inspection and copying by authorized representatives of the DoD or, as applicable, FDA, at reasonable times and in a reasonable manner.

Other individuals and groups may legitimately obtain copies of particular documents or, exceptionally, have access to files, if determined by the Commander, Deputy Commander, or the Human Protections Administrator (HPA). This may include investigators, representatives from cooperative research groups, officials from the FDA and other federal agencies as determined by law and regulations. If rights of access are at all unclear, the HPA will consult with the DDEAMC Staff Judge Advocate and the DDEAMC Privacy Officer.

Department of Defense Instruction "Protection of Human Subjects and Adherence to Ethical Standards in DoDSupported Research", Number 3216.02, November 8, 2011 states:

a. 32 CFR 219 requires all institutions engaged in DoD-conducted or -supported research involving human subjects to retain records for at least 3 years after the completion of the research. Research involving human subjects may be covered by other Federal regulations that impose longer record keeping requirements. The DoD Components may rely on the non-DoD institutions to keep the required records that were generated by the institution, or the DoD Components may make arrangements to transfer the records.

b. The DoD Components shall also retain records regarding the oversight of DoD Component-supported research involving human subjects for at least 3 years after the completion of the research, HRPP education or training program, or other action relevant to the HRPP. Additionally, the DoD Components shall keep all records regarding DoD Component waivers, exemptions, and extensions, and all DoD Component requests for exceptions, waivers, exemptions, and extensions submitted to the ASD(R&E) for action for at least 3 years after the completion of the research.

c. The DoD Components may be required to retain records for longer than specified in paragraphs a. and b. of this section. For example, some Health Insurance Portability and Accountability Act documentation is required to be retained for 6 years (in accordance with DoD

6025.18-R)For complete recordkeeping guidance and instruction, the DoD Components shall consult their respective records disposition schedules.

d. Records maintained by non-DoD institutions that document compliance or noncompliance with this Instruction shall be made accessible for inspection and copying by authorized representatives of the Department of Defense at reasonable times and in a reasonable manner as determined by the supporting DoD Component.

## 7.3 Investigator Records

Investigators and research staff are responsible for maintaining current, complete, and accurate files containing all documents related to human subject studies. Documents pertaining to both the DDEAMC IRB file and the PI file are one in the same in the web-enabled software system with the exception of documents pertaining to the execution of this study (i.e., signed informed consent forms signed HIPAA forms, case report forms, source documents, etc.). These files must contain the following:

1. All approved versions of protocols;
2. All approved versions of consent forms (or documentation of waiver of informed consent or waiver of written informed consent);
3. All approved versions of Health Insurance Portability and Accountability Act (HIPAA) Authorization form or Waiver of Authorization if research involves protected health information;
4. Original signed informed consent documents (ICD) for each subject (until study closure)—must be maintained in a secured location, accessible only to the Principal Investigator (PI) or designated member of the research team; ICDs should be maintained separately from any linking document that would identify subjects with study numbers;
5. Protocol submission form;
6. All IRB-approved recruitment materials;
7. Photographic consent/photographic release form;
8. All approved data collection forms;
9. DDEAMC Commander approval letters (initial and continuing);
10. All approved protocol amendments and related documents;
11. All communications between the Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO) or IRB, the Scientific Reviewers, and the PI;
12. All Correspondence with USAMRMC Human Research Protections Office (HRPO), and other regulatory agencies, as applicable;
13. Continuing Review reports;
14. All reports of deviations, adverse events, or unanticipated problems involving risk to subjects or others;
15. Master subject enrollment log - must be maintained in secured location, accessible to the PI or associate only, and maintained separately from any completed ICDs, Data

collection forms, or any study documents bearing either a subject's name or a subject's study identification number;

16. Subject list (with identifiers) and group assignment code (randomization code)—must be maintained in a separate, secured location away from PHI, accessible to the PI or associate only;
17. Documentation of subject briefings (date, attendees, and outline of briefing) must be maintained in a separate, secured location away from PHI, accessible to the PI or associate only;
18. COI disclosure forms, if required;
19. Data exchange or material transfer agreements (MTA);
20. Copy of Memorandum of Agreement or Cooperative Research and Development Agreement (CRADA).

Individual subjects files where study files identify the subject by name must be separate from study records maintained by the subject number to include signed informed consent forms, HIPAA authorizations, case report forms, source documentation and other documents specifically related to an individual subject will be maintained by the PI. Research records (including data) are the property of DDEAMC and its MTFs covered by the Assurances and shall not be transferred to another entity without prior approval of the DDEAMC Commander.

**Investigator Record Storage**

All PI records must be accessible for inspection and copying by the DDEAMC IRB or authorized representatives of DA or DoD at reasonable times and in a reasonable manner. Access restrictions must continue in force until the records are destroyed.

1. The PI must retain all research-related records for a minimum of three years after the study is completed, terminated, or discontinued unless the research is under the purview of the FDA.
2. For those protocols that involve the use of an investigational drug or device or another FDA regulated test article, the PI is responsible for compliance with 21 CFR312.62 Investigator record keeping and record retention:
   a. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR312.59.
   b. Case histories. An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational drug or employed as a control in the investigation.
   c. Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified IAW 21 CFR Part 312.62(c ).

3. For those protocols that require review under the International Conference on Harmonisation (ICH), the PI is responsible for maintaining the research records per ICH Guidelines 4.9 Records and Reports, Section 4.9.5:

   > Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see section ICH 5.5.12).

4. All HIPAA Authorizations are to be maintained for at least six years.
5. Investigators that deploy or leave DDEAMC or its MTFs covered under the Assurances are required to transfer the research records to a new PI or their Service Chief within their departing MTF. Custody of all original data must be retained by the research division in which they were generated. An investigator who moves to another institution may submit to the Commander a written request to remove copies of the data from the organization. This request must contain an itemized description of the data and must specify where the data will be located in the future. The review and release of the JAG office will be evaluated on a case-by-case basis.

## 7.4 IRB Records

The DDEAMC IRB, through the RRCO, maintains records of all protocols and correspondence submitted to the IRB and minutes from all convened board meetings. The RRCO currently maintains only electronic files. The RRCO secures records in a restricted-access web-enabled software system for IRB records. Access to IRB records is limited to the IRB, RRCO staff, authorized IRB consultants, the Commander or individuals acting on his behalf, and officials of DoD regulatory agencies, including the Department of the Army Human Research Protections Office (AHRPO) and the U.S. Army Medical Research and Materiel Command, Office of Research Protections (ORP).

Research investigators and those individuals which the investigator has granted access, will have reasonable access to files related to their research. Others who are not listed as key personnel on a protocol may only have access to file documents with explicit permission of the principal or lead investigator. All other access to DDEAMC IRB records is limited to those who have legitimate need for them, as determined by the HPA.

### The web-enabled software system Implementation for Electronic Storage of Research Protocols

All new protocols received after April 9, 2009 must be submitted via the web-enabled software system for electronic IRB records and the associated documentation is maintained within this system where the web-enabled software system for electronic IRB records assigns a specific identifier for each protocol. Any protocols that were already approved or active as of April 9, 2009 require the PI to “create” an associated project, if not already done, and scan all documents into the web-enabled software system for electronic IRB records at the time of continuing

review. Previously the DDEAMC IRB maintained a separate file for each research protocol received for review which is detailed later in this policy.

Each protocol folder contains the documents related to the protocol to include those submitted by the research team as well as the IRB members and DCI staff.

**Hard Copy Protocol Files**

In May 2009 all hardcopy protocol files were organized to be maintained in multi-tab classification folders in submission order with the most recent submissions on top. The DDEAMC IRB records for a protocol were organized to permit reconstruction of a complete history of all IRB actions related to review and approval of the protocol. Some protocols consisted of multiple folders and were labeled "x of y" to alert RRCO staff that there are multiple folders. Each of these files, for non-exempt human subject research, contains the following labeled tabbed dividers, if applicable:

- General Correspondence
- DCI and DDEAMC IRB Official Correspondence
- USAMRMC ORP CIRO/HRPO Official Correspondence
- Non-DDEAMC IRB Actions (WRAMC IRB, etc.)
- Protocol Review Checklists
- Consent Form
- Amendments
- Continuing Reviews
- Other
- Required Reports

These hard copy records are in process for scanning and electronic maintenance and storage. They will be maintained for fifty years.

**IRB Membership Roster**

The RRCO maintains the DDEAMC IRB membership roster as noted in Chapter 1 Framework. The IRB roster is filed with the Department of the Army Human Research Protections Office (AHRPO). AHRPO is promptly notified of any changes in IRB membership.

**IRB Membership Documentation**

The RRCO maintains documentation related to the DDEAMC IRB membership on the secure Y drive which has limited access. This documentation includes;

- Current membership roster
- Current resumes or curriculum vitae (CV) to include information related to earned degrees, indication of experience such as board certifications, licensures, registrations, or other relevant experience sufficient to describe each member's chief anticipated contribution to IRB deliberations.
- Documentation of CITI completion and/or DHHS OHRP Human Assurance Module training is also maintained on the secure drive.

- Appointment letters.

**Minutes of Convened IRB Meetings**

The DDEAMC IRB meeting minutes will record that all regulatory requirements for review of research were considered and discussed. The minutes should enable a reader who was not present at the meeting to determine exactly how and with what justification the DDEAMC IRB arrived at its decisions. They should also provide the DDEAMC IRB itself with sufficient detail to help it reconstruct its discussions at a later date, if necessary.

Detailed minutes of each DDEAMC IRB meeting shall be kept by the designated recorder under the supervision of the HPA. The format and content will comply with the federal regulations and is outlined in Chapter 6 Policy #1 IRB.

The DDEAMC IRB minutes are subject to the Freedom of Information Act (FOIA); therefore, DDEAMC IRB meeting minutes are written impersonally, and opinions expressed by members are not attributed to them. Members are only identified by name when they are recused from a particular review or leave the meeting for any reason.

Each protocol discussed indicates the DDEAMC IRB protocol number and title. Copies of any handouts distributed during the meeting will be attached to the minutes. Minutes are filed chronologically.

**Documentation of Exemption Determinations**

The web-enabled software system program includes files containing documentation for protocols determined to be exempt under 32 CFR 219.101(b), including documentation of the basis for the finding and the applicable exemption category(ies) number(s), who made the determination, and when. Documentation that the exemption criteria has been verified as correct by the IRB is documented by the reviewer's concurrence in the DDEAMC IRB protocol file that the activity described in the investigator's request for exemption satisfies the conditions of the cited exemption category per 32 CFR 219.101(b).

**Documentation of Expedited Reviews**

The web-enabled software system includes the documentation for protocols to include the:

1. Permissible category or categories of expedited review that apply (e.g., collection of data through non invasive procedures per 32 CFR 219.110(b) (1) Category 4)
2. Research is minimal risk
3. Why
4. By Whom
5. When
6. Any attending HIPAA or regulatory determinations

**Documentation of IRB Actions**

Documentation related to the IRB actions on individual protocols are maintained in the web-enabled software system. The determination letters and minutes list the documentation approved. Auditors are provided one-on-one assistance to navigate the web-enabled software system.

## 7.5 HRPP Administration Records

The RRCO maintains written up-to-date policies, procedures, forms and templates, and guidance documents for the HRPP, to include this HRPP Manual in The web-enabled software system. Approved copies are maintained in the HPA office and scanned to the Y drive.

Copies of all reports to USAMRMC HRPO and AHRPO are maintained on-site indefinitely.

The HPA maintains original signed copies of the following:

1. The DDEAMC DDEAMC's DoD A10015 and DHHS OHRP FWA #00004975 Assurances,
2. IRB Authorization Agreements, Memorandums of Understanding (MOUs) and DoD Institutional Agreements for Institutional Review Board (IRB) Review,
3. This HRPP Operations Manual and related policies, procedures, and Standard Operating Procedures (SOPs),
4. Review committee member appointment orders.

### Education and Training Records

Education is required for all individuals in the HRPP process. The RRCO staff maintains records of completed human research protections training (and HIPAA training when indicated) in the web-enabled software system for the following:

1. Investigators
2. Coordinators
3. IRB Chair, Vice-Chair and members
4. RRCO staff
5. Institutional officials

The HPA retains copies of all training material distributed to IRB members, as well as records of all local seminars and conferences attended by any member. Members are encouraged to send copies of any completion certificates from online tutorials or other training sessions to the Administrator.

GCP training is required IAW AR 40-7 for all investigators involved in FDA regulated clinical trials.

### Budgetary and Accounting

Documentation related to budgetary and accounting issues will be maintained as required and with limited access.

## 7.6 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.

5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 8: Research Risks and Benefits

## 8.1 Purpose

The purpose of this policy is to provide definitions and guidance related to the assessment of research risks and benefits as a part of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 8.2 Background

The main emphasis of any IRB review is to protect the rights and welfare of participants involved in human subject research (32 CFR 219.109). It is understood that all human research carries a certain amount of risk to the subjects. There are multiple cases in history where research did not meet the basic tenets of The Belmont Report. The DDEAMC HRPP is designed and carried-out with multiple layers of checks and balances to ensure risks to research subjects are avoided or mitigated. All DDEAMC and its covered military treatment facilities (MTFs) under the Assurances and the staff (military, civilian and contractors) involved in the conduct, review, or oversight of research are responsible for ensuring that the rights, welfare, health, and safety of research subjects and staff are protected. The "Common Rule" IAW 32 CFR 219 requires all IRBs to ensure that:

- Risks to subjects are minimized and
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be reasonably expected to result

## 8.3 Overview

One of the primary responsibilities of the DDEAMC Institutional Review Board (IRB) is to assess the possible risks and anticipated benefits of research. The risk classification may influence the mode of review (expedited versus convened committee), specific regulatory findings (such as Subpart D findings, requirement for research monitor, waiver of informed consent, etc.) the frequency of review, the level of post-approval monitoring, and other factors. In addition, once risks and benefits have been identified, the DDEAMC IRB is responsible for ensuring that the risks of study participation are minimized to the greatest extent possible and that the risks are reasonable in relation to the anticipated benefits to the subjects themselves, to others in similar conditions or with similar needs, or to society in general.

## 8.4 Definitions

**Risk -** As defined in the federal regulations, risk is the probability of harm (physical, psychological, social, legal, or economic) occurring as a result of participation in research. Both the probability and the magnitude of possible harm may vary from minimal to significant. The Federal regulations only define minimal risk (32 CFR 219.111).

**Minimal Risk** IAW with DoDI 3216.02, when evaluating risk, the phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" in the definition of minimal risk established at32 CFR 219.102(i) inserted below, shall not be interpreted to include the inherent risks certain categories of human subjects

face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain). Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (32 CFR 219.102).

**Benefit** - a valued or desired outcome or an advantage from the research.

## 8.5 IRB Considerations

Per Federal regulations (32 CFR 219. 111 and 219.116), the DDEAMC IRB is required to make determinations on the items listed below when assessing risks and benefits of a research protocol involving human subjects. The IRB is required to:

- Identify the risks directly related to the research and its procedures, (excluding possible risks related to a standard of care procedure that occurs in close proximity to the study procedures)
- Determine that the risks will be minimized;
- Assess the degree of risk that participation presents to subjects (not greater than minimal risk vs. greater than minimal risk);
- Identify the probable benefits to be derived from the research;
- Determine that the risks are reasonable in relation to the benefits to subjects, if any, and the importance of the knowledge to be gained;
- Assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits;

## 8.6 Investigator Responsibilities

The DDEAMC IRB relies on the investigators to address the risks and benefits presented by the research within the written protocols and any supporting consent documents. The protocol and consent form must clearly distinguish procedures which are “standard of care” from those which are conducted solely for research purposes. Investigators bear the primary responsibility for distinguishing between the standard of care and the research procedures.

Evaluation of risks goes beyond looking at the study procedures and the vulnerability of the subjects, but must also include an evaluation of the physical setting where the study procedures will be conducted and the resources available to manage adverse events. .

Investigators are advised to address the following questions when designing the research and writing the protocol

a. Have the risks to subjects been minimized?
b. Is the investigation sound and will the information gained be useful?
c. Is the risk to the subjects reasonable in relation to the anticipated benefits?
d. Does the protocol provide sufficient information to justify the risk/benefit ratio?
e. Have the discomforts and risks been appropriately minimized?
f. Is the selection of research subjects equitable?

g. Is informed consent being obtained and documented?
h. Are there appropriate provisions to ensure confidentiality of data and privacy for subjects?
i. Are additional safeguards in place to protect a vulnerable subject population?
j. Does the study include a valid plan to monitor the safety of the subjects?

The DDEAMC IRB will concentrate on the immediate or reasonably foreseeable risks of the research rather than the risks associated with the long-term outcome or consequences of applying the knowledge gained from the research. The Federal regulations state that the IRB should not consider possible long-range effects of applying knowledge gained in research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility [32 CFR 219.111(a)(2)].

## 8.7 Types of Research Risks

Research risks can be categorized broadly as physical, psychological, social, economic or legal. These categories are not mutually exclusive and more than one type of harm might be present in a given research study. Investigators and IRB members must think through all the risk possibilities, however rare, so that courses of action can be planned to prevent harm or to quickly and effectively manage any incident.

### Physical Risk

Physical risk includes physical discomfort, pain, injury, illness or disease brought about by the methods and procedures of the research. Physical adverse events that result from study procedures or interventions can be transient or permanent and they may range from minor to severe. This may include such diverse harms as myocardial infarction related to maximal exercise treadmill testing to discomfort related to the requirement to lie still in an MRI machine for an extended period.

### Psychological Risk

Participation in research may result in undesired changes in thought processes and emotion (anxiety, stress, fear, confusion, embarrassment, depression, guilt, shock, loss of self-esteem, altered behavior). These changes may be experienced during the research situation or later. Most psychological risks are minimal or transitory, but some research has the potential for causing serious psychological harm.

Stress and feelings of guilt or embarrassment may arise simply from thinking or talking about one's own behavior or attitudes on sensitive topics such as alcohol or drug use, sexual behavior, selfishness, and violence. These feelings may surface when the subject is being interviewed or filling out a questionnaire. Such feelings may occur when subjects feel they have been treated as means to an end or their concerns have not been adequately addressed. Psychological harm is more likely when behavioral research involves an element of deception.

### Social Risk

Some invasions of privacy and breaches of confidentiality may result in alterations in relationships with others that are to the disadvantage of the subject, including embarrassment,

loss of respect of others, labeling or stigmatizing with negative consequences, or diminishing the subject's opportunities and status in relation to others.

**Economic Risk**

Economic risks include payment by subjects for procedures, transportation, or childcare; loss of wages or income; and damage to employability.

**Legal Risk**

Risk of criminal prosecution or civil lawsuit may occur when research methods reveal that the subject has or will engage in conduct for which the subject or others may be criminally or civilly liable.

**Invasion of Privacy**

Invasion of privacy concerns access to a person's body or behavior without consent. In the research context, it usually involves either covert observation or "participant" observation of behavior that the subjects consider private.

**Loss of Confidentiality**

Confidentiality of data concerns safeguarding information that has been given voluntarily by one person to another. Confidentiality of research data is presumed and must be maintained unless the investigator obtains the express permission of the subject to do otherwise. A breach of confidentiality may result in the psychological, social, economic and legal harms outlined above. This risk continues to be important after the research is complete and should have an impact on the study design in regards to the identifiers needed for the research.

## 8.8 Types of Research Benefits

There are two types of research benefits – one to subjects and one to society.

**Benefits to Subjects**

There are two types of benefits to research subjects and they are outlined in detail below:

**Direct Benefits**

Research may provide subjects with treatment, diagnosis, or examination for an illness or condition. For example, potential benefits include receiving clinically significant information that could be used to influence health care, receiving counseling as part of the research, or gaining access to experimental interventions that may improve the participant's health status. These benefits are to be contrasted with unplanned or unanticipated benefits that are secondary to the objectives of the study. Secondary direct benefits could occur from increased self-awareness obtained through data collection methods that leads to lifestyle change or pursuit of treatment. When identifying potential direct benefits to subjects, the DDEAMC IRB considers only those that might result strictly from study participation.

**Indirect Benefits (also called collateral benefits)**

Individuals might benefit indirectly from participation in research by experiencing increased social contact, sharing information with another person, or gaining personal satisfaction from participating in the research. Indirect benefits typically are not planned by investigators and do not relate to the study objectives. In addition, they are likely to vary among research subjects. Although these benefits should be acknowledged, they should not weigh in the judgment of the DDEAMC IRB regarding the balance of risks and potential benefits to subjects. To the extent that indirect benefits can be anticipated, however, investigators should design research to increase them.

**Benefits to Society**

This classification of risk is the potential gain of new knowledge that may be generalized to a large population group or society as a whole.

## 8.9 Interpretation and Minimization of Research Risks

**Potential Harms Versus Discomforts**

The DDEAMC IRB should not use anecdotal aversion to an experience when assessing the risks related to research. The IRB must distinguish between those risks that could be considered potential harms of the study and those risks that are simply discomforts for subjects. To ascertain the risk category, the IRB should concentrate on those aspects of a study that present potential harm to the subjects IAW with the "Common Rule". Participation in a study that may cause limited discomfort may be recommended for approval by the IRB as not greater than minimal risk because an autonomous person may determine whether or not he or she is willing to endure the discomfort associated with the research.

All research-related risks—potential harms, discomforts, and inconveniences—must be discussed in the informed consent document. However, the DDEAMC IRB's responsibility is to rely on the regulatory definition of minimal risk.

Risks may be reduced in a variety of ways, for example, by assuring that:

- The study design is valid;
- The research team has sufficient expertise and experience to conduct the research
- Staffing levels are adequate;
- The projected sample size is sufficient to yield useful results;
- Criteria for subject enrollment and withdrawal are appropriate;
- Prospective subjects at undue risk of harm are excluded;
- Subjects are allowed to stop anytime that they feel uncomfortable;
- Subjects are adequately monitored;
- Data are collected without identifiers when possible;
- Procedures are in place to protect the confidentiality of the data (e.g., encryption, codes, passwords); and
- Identifiers and master keys to coded data are destroyed as soon as possible.

All personnel performing risky or invasive procedures with research subjects will have been granted specific procedural privileges based on review of their credentials and if appropriate, additional training.

## 8.10 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 9 - Subject Selection and Recruitment

## 9.1 Purpose

The purpose of this policy is to provide guidance on the selection and recruitment of research subjects from vulnerable populations by research teams that fall under the Human Research Protection Program (HRPP) at Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 9.2 Background

Historically there were multiple abuses of research subjects based on their accessibility or ease of use. The development of federal regulations to specifically protect certain categories of potential subjects as members of vulnerable populations has increased the research community's understanding of critical issues that are related to the recruitment, inclusion, and retention of these individuals in research studies. 45 CFR part 46, part B identifies pregnant women, fetuses and neonates; 45 CFR part 46, part D children including wards of the State; 45 CFR part 46, part C prisoners; 21 CFR 56 Part 111, handicapped, or mentally disabled persons; and economically or educationally disadvantaged persons as vulnerable populations for research.

The recruitment of subjects is actually the first step in any informed consent process and sets the tone for all future communications with the potential subject. The issues related to the type and depth of information given to the subject as well as their comprehension of that information is the cornerstone of the communication process. Each subject must be able to determine their own voluntariness is participating in research and should not feel coerced or any undue influence to participate.

## 9.3 Definitions

**Children -** Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

**Dead Fetus -** A dead fetus is a fetus which does not exhibit either heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord if still attached.

**Delivery –** Delivery means the complete separation of the fetus from the woman by expulsion, extraction, or any other means.

**DoD Personnel -** IAW DoDI 3216.02, DoD civilian employees and members of the military services.

> DoD civilian employee – An individual meeting the definition of "employee" consistent with section 2105 of Reference (m) in the DoDI 3216.02 to include employees of DoD Non-Appropriated Fund Instrumentalities; DoD civilian employees filling full-time, part-time, intermittent, or on-call positions; and individuals serving under personal services contracts consistent with section 2.101 of Reference (n) in the DoDI 3216.02. It excludes employees of contractors (other than personal services contractors) and foreign nationals of host countries.

Service members – Individuals appointed, enlisted, or inducted for military service under the authority of the Department of Defense. The Military Services as the Army, the Navy, the Air Force, the Marine Corps, the Coast Guard, and the Reserve Components, which includes the Army and the Air National Guards of the United States. Members of the Reserve Components are included when in a duty status.

**Economically or Educationally Disadvantaged Persons** - Persons placed at special risk by socioeconomic and educational background. Economically disadvantaged persons include those persons who struggle to provide basic necessities for themselves and their families or communities.

**Fetus -** A fetus is defined as the product of conception from the time of implantation until delivery.

**In Vitro Fertilization -** In Vitro Fertilization is any fertilization of human ova, which occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.

**Neonate -** A neonate is an infant aged one (1) month or less.

**Non-Viable Neonate -**Non-viable neonate means the same as a non-viable fetus and is not able to survive to the point of independently maintaining heart and respiration after delivery.

**Ombudsman –** A person who acts as an impartial and objective advocate for human subjects participating in research.

**Pregnancy -** Pregnancy is the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

**Viable Neonate -** A viable neonate means to survive to the point of independently maintaining heart beat and respiration after delivery (given the benefit of available medical therapy).

**Vulnerable –** Subjects who fit into any of the following categories IAW Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) 45 CFR 46 subparts B, D and D as well as FDA 21 CFR 56.111(b):

- Pregnant Women, Fetuses and Neonates (Note that DoDI 3216.02 applies Supbart B differently than DHHS does. The more restrictive DHHS regulations must be followed if DHHS is providing support.)
- Children including Wards of the State
- Prisoners
- Handicapped, or Mentally Disabled Persons, or
- Economically or Educationally Disadvantaged Persons

Other subject groups may be considered to be vulnerable based upon the facts of the situation and local context. Such groups include, but are not limited to, DoD personnel (see definition above).

## 9.4 Selection of Research Subjects

The Belmont Report specifically addresses the principle of justice in the selection of research subjects at two levels: the social and the individual. Investigators must fairly select their research subject population and not burden a potential population because of convenience, ease of access, etc.

### Equitable Selection

"Distributive justice," the third principle of the Belmont Report, requires the fair selection of research subjects and the equitable distribution of the burdens and benefits of research. Selection of research subjects must be equitable within the confines of the study.

Unless justified by the science, equitable selection of subjects means:

- Subjects shall not be excluded from research on the basis of criteria such as gender, sexual orientation, race, national origin, religion, creed, education, or socioeconomic status.
- Subjects shall not be included in research simply because of their easy availability, compromised position or because of racial, social, gender, economic, or cultural biases.
- One group of research subjects shall not be systematically selected to bear the burdens of research that will benefit another group.
- A group of subjects shall not be systematically excluded from participation in research that could benefit that group.

To protect potentially vulnerable subjects, the National Commission for the Protection of Human Subjects has recommended a hierarchy of preference in the selection of subjects for research:

- Adults before children;
- Competent individuals before incompetent individuals;
- Non-institutionalized individuals before institutionalized individuals.

The Commission also believed that those who are already burdened (e.g., by disabilities or institutionalization) should not be asked to accept the burdens of research unless other appropriate subjects cannot be found.

## 9.5 Pregnant Women, Fetuses and Neonates

This group of potential subjects, pregnant women, fetuses and neonates) is considered a vulnerable population and the governing regulation for research is Subpart B 45 CFR 46.201-.207 as required by DoD 3216.02 section 4.4.1.

### Pregnant Women

Federal regulations [45 CFR 46.207] stipulate that any research involving pregnant women in any manner must have specific approval for their participation. Additional safeguards may be requested by the DDEAMC IRB to avoid undue influence and coercion. There are specific requirements and exceptions to the consent requirements in these situations such as noting research team consideration of the following issues in the protocol (45 CFR 46.204) states that

pregnant women, fetuses and neonates may be involved in research if **all** of the following conditions are met:

a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

**Risk**

a. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or,

   If there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

b. Any risk is the least possible for achieving the objectives of the research;

**Consent**

a. If the research holds out the prospect of :
   - Direct benefit to the pregnant woman,
   - The prospect of a direct benefit both to the pregnant woman and the fetus, or
   - No prospect of benefit for the woman nor the fetus when the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means,

The consent of the pregnant woman is obtained in accord with the informed consent provisions of 45 CFR 46 Sub-Part A.

b. If the research holds out the prospect of direct benefit solely to the fetus then:
   - The consent of the pregnant woman and the father of the fetus is obtained in accord with 45 CFR 46 Sub-Part A.
   - Except that the consent of the father of the fetus need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest. NOTE: Unavailability will not necessarily preclude a deployed Soldier in theater from providing his consent based on the technology available.

c. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
d. For children as defined in 45 CFR 46.402(a) who are pregnant; assent and permission obtained in accord with the provisions of subpart D of 45 CFR 46;

**Exclusions**

a. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
b. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
c. Individuals engaged in the research will have no part in determining the viability of a neonate.

**Research involving Neonates**

a. Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

   1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

   2. Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

   3. Individuals engaged in the research will have no part in determining the viability of the neonate.

   4. The requirements of paragraph (b) or (c) of this section have been met as applicable.

b. Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

   1. The DDEAMC IRB determines that:

      i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

      ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

   2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent or either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

c. Nonviable neonates. After delivery nonviable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

   1. Vital functions of the neonate will not be artificially maintained;

   2. The research will not terminate the heartbeat or respiration of the neonate;

   9. There will be no added risk to the neonate resulting from the research;

   4. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

   5. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of 45 CFR 46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one

parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

d. Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

**46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.**

a. Research involving any of the following, after delivery shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities:

- The placenta;
- The dead fetus;
- Macerated fetal material; or
- Cells, tissue, or organs excised from a dead fetus,

b. If information associated with material as described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or indirectly through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part (aka Common Rule) are applicable.

**9.6 Children**

Federal regulations [21 CFR Parts 201, 312, 314 and 601and 45 CFR46 (OHRP) subpart D .401-409] stipulate that any research involving children or pediatric subjects in any manner must have specific approval for their participation. The age of majority for consent in these states and territory is:

1. Georgia = Eighteen (18)
2. Alabama = Nineteen (19)
3. Florida = Eighteen (18)
4. Kentucky = Eighteen (18)
5. Mississippi = Twenty-one (21)
6. South Carolina = Eighteen (18)
7. Puerto Rico = Twenty-one (21)

**Research Consent of Minors**

Most states and territories do not have specific laws that address the consenting of minors for research. As such, the usual process has been to apply laws that relate to medical treatment. In Georgia, the following may consent for the treatment of minors and note that the consent of only one person is required unless specifically requested by the IRB:

1. Any parent for his/her minor child.
2. Any person temporarily standing "in *loco parentis*," whether formally serving or not, for the minor under his/her care.

9. In the absence of a parent, spouse, legal guardian, or person standing in *loco parentis*; any adult may consent to treatment for his/her minor brother or sister; or a grandparent for his/her minor grandchild.

Exceptions to the above rule are as follows:

1. A minor who is a parent may consent to the treatment of his/her own child.
2. Married minors may consent to treatment for themselves or their spouses.
9. Any female, regardless of her age or marital status, may consent to her own treatment in connection with pregnancy, the prevention of pregnancy, or childbirth.
4. A minor who is, or professes to be, afflicted with a venereal disease may consent to his/her own treatment.
5. A minor may consent to his/her own treatment for drug abuse.

When obtaining informed consent for treatment, physicians should use good judgment and inquire to satisfy themselves that the person purporting to be the guardian or in "*loco parentis*" honestly has that relationship with the minor. Research may require the additional consent of an advocate or other representative of the minor. Each of these instances will be discussed on a case-by-case basis.

Georgia law provides the following protection for good faith efforts to obtain consent for the treatment of minors: "Any person acting in good faith shall be justified in relying on the representations of any person purporting to give consent, including, but not limited to, his identity, his age, his marital status, his emancipation, and his relationship to any other person for whom the consent is purportedly given." O.C.G.A. Section 31-9-6(c).

The Department of Defense Instruction “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research”, October 20, 2011 states:

For purposes of legal capacity to participate in DoD-conducted or -supported research involving human subjects, all active duty Service members and all Reserve Component members in a Federal duty status are considered for purposes of this Instruction to be adults. The participation of such members is not subject to requirements of paragraph 7.d. of this enclosure or subpart D of Reference (h) regarding research involving children or minors. When Service members are under 18 years of age, students at Service Academies, or trainees, the IRB shall carefully consider the recruitment process and the necessity to include such members as human subjects.

**Other States or Territories**

The state or territorial laws applicable to the other areas in the DDEAMC catchment will be added as the issues present themselves.

**Wards**

Children who are wards of the state or any other agency, institution or entity who are proposed to participate in research present additional responsibilities for inclusion in research projects.

**9.7 IRB Member Responsibilities**

In making their assessment, the DDEAMCIRB should take into account the purposes of the research, the setting in which the research will be conducted, the selection criteria and the

recruitment procedures. The IRB should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. In some situations, military populations are vulnerable populations. The IRB should ensure that additional safeguards are included in the study to protect the rights and welfare of these subjects.

Questions to ask when reviewing subject selection are:

1. Who are the subjects? Are they vulnerable?
2. Are the subjects appropriate for the research or are they a convenience sample?
3. Are the sufficient numbers available to conduct the research?
4. What are the inclusion/exclusion criteria?
5. Should certain subjects be excluded for safety or scientific reasons?
6. Are there sufficient safeguards in place to protect vulnerable subjects?

The DDEAMC IRB should answer the following questions when reviewing research involving children and/or wards:

1. Who are the subjects?
    a. Children
    b. Wards
    c. Parent(s)/guardian(s)
    d. Advocate(s)
    e. Others
    f. All
2. Is the study FDA regulated?
    a. If no, is this study exempt from the Common Rule, and thus exempt from Subpart D?
3. Is the study regulated by 10 USC 980 as discussed previously?
    a. If yes, is there direct benefit to the children subjects?
4. What are the risks this study presents to the subjects, and how are these risks mitigated?
5. What is the level of risk presented by the study to subjects?
    a. Does the study present no greater than minimal risk (NGTMR) to the subjects?
    b. Is the study greater than minimal risk (GTMR)?
        i. If yes, is there the prospect of a direct benefit to the individual subject?
        ii. Is the risk justified by the anticipated benefit to the subjects?
        iii. Is the relation of the anticipated benefit to the risk at least as favorable to the subjects as that presented by available alternative approaches?
    c. Is the risk a minor increase over minimal risk?
        i. Is yes, does the intervention or procedure present experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations?
        ii. Is the intervention of procedure likely to yield generalizable knowledge about the subject's disorder or condition with is of vital importance for the understanding or amelioration of the subjects' disorder or condition?
6. What is the appropriate Subpart D category for reviewing this research?
7. Are the necessary elements of parental permission/assent met?
    a. If children are wards and the study is approved under 45 CFR 46, have the requirements of 45 CFR 46.409 been met?
8. Have the other Section 111 criteria necessary for approval been met?

## Federal Regulations for Guidance to the IRB Members

The federal regulations (45CFR 46 Sub-Part D) provide the following guidance when reviewing a research project that involves children or wards:

### 45 CFR 46.404 Research not involving greater than minimal risk.

No greater than minimal risk to children is presented.

Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 CFR 46.408.

### 45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

More than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, and

The risk is justified by the anticipated benefit to the subjects; and

The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408

### 45 CFR 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

More than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, and

The risk represents a minor increase over minimal risk; and

The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; and

The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 CFR 46.408

### 45 CFR 46.408 Requirements for permission by parents or guardians and for assent by children

***Assent***

Adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent.

In determining whether children are capable of assenting, the DDEAMC IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the DDEAMC IRB deems appropriate. If the DDEAMC IRB determines that the capability of some or all of the children is limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the contest of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the DDEAMC determines that the subjects are capable of assenting, the DDEAMC IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with 45 CFR 46.116.

When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

***Permission***

Adequate provisions are made for soliciting the permission of each child's parents or guardian.

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404 or 45 CFR 46.405. Where research is covered by 45 CFR 46.406 and 45 CFR 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

The research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children).

In such instances, the IRB may waive the consent requirements provided an appropriate mechanism or protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status and condition.

Permission by parents or guardians shall be documented in accordance with and to the extent required by 45 CFR 46.117.

**45 CFR 46.409 Wards**

Children who are wards of the state or any other agency, institution or entity are proposed to be included in research approved under 45 CFR 46.406 or 45 CFR 46.407, and

The research is related to their status as wards; or

Conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards.

The IRB has appointed an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or *in loco parentis*.

One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

### 9.8 Cognitively Impaired Persons

The FDA regulations define that handicapped, or mentally disabled persons, are vulnerable subjects. At DDEAMC and its MTFs covered under the Assurances, these are defined as a cognitively impaired person having either:

- A psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders),
- An organic impairment (e.g., dementia),
- Or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished.

In addition, persons under the influence of or dependent on drugs or alcohol, suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

The major ethical concern in research involving individuals with these types of disorders or impairments is that their disorders may have an impact on their capacity to understand the information presented as well as their ability to make a truly informed decision about participation in the research. Some individuals with such disabilities may be residents of institutions responsible for the individual's total care and treatment. This dependence on the institution may have an impact on their ability to voluntarily participate in research (e.g., these individuals may agree too readily to requests for their "cooperation" or may be vulnerable to perceived or actual pressures for fear of being denied services.) The DDEAMC IRB must review several areas and their potential for coercion when reviewing research involving cognitively impaired persons:

- Are these individuals the primary population for this research?
- Are there adequate protections for privacy and confidentiality of information?
- How are issues of consent and competence addressed?

There should be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.

A surrogate whose ***primary*** interest is the patient's welfare may give informed consent if conditions are met for cognitively impaired subjects.

Competency is commonly judged by the subject evidencing a choice with regard to research participation, through factual understanding of issues including the rational manipulation of information as well as the appreciation of the nature of the research project. If competency is an issue, it must be acknowledged in the research protocol and the procedures used to evaluate competency must be described in detail.

## 9.9 Economically or Educationally Disadvantaged Persons

Incentives for participation as a human research subject are common but the investigator must include in the research design that any incentives for participation must not take away or remove the person's ability to decline participation in the research.

These incentives include but are not limited to:

- Medical care
- Remedial education and
- Financial remuneration.

Educationally disadvantaged persons may have:

- Educational deficits
- Learning disabilities, such as an inability to read, or
- Cultural backgrounds that limit communication with a researcher.

The investigator is responsible for ensuring that all subjects are fully informed.

## 9.10 Payment or Compensation to Research Subjects

Payment or compensation for research subjects may be acceptable if (1) the possibility of coercion or undue influence is minimized, and (2) the compensation is considered a recruitment incentive, not a benefit, in accordance with DoD regulations at 32 CFR §219.116. Compensation for participation is not an obligation of the researcher toward the participant. Payment may be offered, but is not required.

Research subjects may be compensated for their time and effort and reimbursed for out-of-pocket expenses related to study participation, such as travel and parking. Compensation, when offered, should be based on a reasonable consideration of the duration of time spent in preparation for, participation in, and recovery from, research interventions, in addition to the effort expended during the research activities.

Compensation should not be used as a "benefit" to offset risks (either quantitative or qualitative) associated with the research.

Credit for payment is to be pro-rated according to the amount of time devoted to the project and will not be contingent only upon the participant completing the study. Particularly where discomforts, stress, or risks are involved, it is not acceptable to withhold all compensation from an individual who made a good faith effort to participate, but withdrew prior to completion of all of the study procedures. Any amount paid as a bonus for completion should be reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.

The research team should decide, based on the subject population**,** the method and delivery of payment. The DDEAMC IRB will review the payment method and delivery to determine if it is appropriate.

a. DoD-Conducted Research Involving Human Subjects
(1) When the Human Subjects Are On-Duty Federal Personnel
(a) Federal personnel (civil servants or Service members) participating as human subjects in DoD-conducted research while on duty (i.e., not on leave and participating during their duty

hours) may be compensated up to $50 for each blood draw if the research meets the purpose of section 30 of title 24, U.S.C. (Reference (q)). Payment for blood draws may come directly from a Federal or non-Federal source. By permitting compensation for blood draws, Reference (q) provides an exception to section 5536 of Reference (m), which prohibits Federal personnel from being paid by any source other than their regular Federal salaries while they are on duty.
(b) Federal personnel participating as human subjects in DoD-conducted research while on duty may only be compensated for blood draws as described in this paragraph and may not be otherwise compensated for general research participation.

(2) When the Human Subjects Are Off-Duty Federal Personnel
(a) Federal personnel (civil servants or Service members) participating as human subjects in DoD-conducted research while off duty may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). Payment for blood draws may come from a Federal or non-Federal source.
(b) Additionally Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

(3) When the Human Subjects Are Not Federal Personnel
(a) Non-Federal personnel participating as human subjects in DoD-conducted research may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). Payment for blood draws may come directly from a Federal or non-Federal source.
(b) Additionally non-Federal personnel may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research. Payment for general research participation may come directly from a Federal or non-Federal source.

b. Non DoD-Conducted Research Involving Human Subjects
(1) When the Human Subjects Are On-Duty Federal Personnel
(a) Federal personnel (civil servants or Service members) participating as human subjects in research conducted by a non-DoD institution (whether or not the research is Federally funded) may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). By permitting compensation for blood draws, Reference (q) provides an exception to section 5536 of Reference (m), which prohibits Federal personnel from being paid by any source other than their regular Federal salaries while they are on duty.
(b) Federal personnel participating as human subjects in non-DoD-conducted research while on duty may only be compensated for blood draws as described in this paragraph and may not be otherwise compensated for general research participation, even if the research is not Federally funded or conducted.

(2) When the Human Subjects Are Off-Duty Federal Personnel
(a) Federal personnel (civil servants or Service members) participating as human subjects in Federally-funded human subject research conducted by a non-DoD institution may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q).

However, if the research is not Federally funded, the human subjects may be compensated for blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the blood draw unless it is prohibited by this Instruction or another policy (i.e., the $50 limitation per blood draw does not apply).
(b) Additionally Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for general research participation must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

(3) When the Human Subjects Are Not Federal Personnel
(a) Non-Federal personnel participating as human subjects in DoD-funded research may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q).
(b) Additionally non-Federal personnel may be compensated for participation in DoD-supported research for other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research. Payment for general research participation may come directly from a Federal or non-Federal source.

**IRB Review of Compensation Plan**

The IRB will review compensation plans to ensure that payments to research subjects provide fair compensation without undue pressure (financial coercion) to participate. Excessive monetary compensation may cause subjects to undertake risks or discomforts that they otherwise would not assume. This unfairly targets subjects of lower socioeconomic groups and places more of the "risk burden" of research on these groups.

**Payment to Children**

Issues to consider when recruiting children are:

1. Non-custodial parent
2. Who will receive payment?
3. Are gift cards better than cash and if so, to which store? If the subjects live in a rural area, then the supercenter may not be conveniently located but a smaller chain may be more convenient for the subjects.

**Payment to Cognitively Impaired**

Issues to consider when recruiting individuals who are cognitively impaired are:

1. Is the individual in charge of their financial affairs or is there an appointed guardian or trustee?
2. Who will receive payment?
3. Is the payment appropriate for the potential subject population? For example, if the study will recruit schizophrenic patients who are homeless in the inner city, then the selection of a large supercenter that is usually located in the suburbs may be inappropriate.

### Payment Plan

Investigators who wish to pay research subjects must indicate their protocol payment plan and the justification for such payment and, in addition, must do the following:

- Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
- State the terms of the subject participation agreement and the amount of payment in the consent form;
- Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the individual to volunteer for the research study.

If the study requires multiple visits, a plan for pro-rating payments in the event of participant withdrawal should be considered.

The consent form must specifically describe payment and/or compensation that the participant will receive as a result of participation in the study. The payment plan should clearly describe the amount or portion of compensation that will be received for each study milestone, as well as the total amount to be paid. Differentials in payment among participant groups (e.g., military versus civilian) may require separate consent forms for each group.

***Note:*** *Payment or other compensation for participation is not considered to be a benefit and must be addressed in a separate section of the protocol and consent document.*

## 9.11 Submission Requirements for Investigators

### General Information

Every protocol must contain a section that describes the population and participant selection criteria and methods. The protocol must describe

- The characteristics of the targeted subjects/participants, including gender, age ranges, ethnic background, and health or treatment status
- The criteria for selection and exclusion
- Whether the study targets or excludes a particular gender or ethnic or racial group
- Where subjects will be found and how they will be recruited
- Why a particular population is being used

Investigators must also justify any proposed involvement of disproportionate numbers of racial or ethnic minorities or vulnerable groups and detail any extra precautions taken to safeguard the rights and welfare of subject populations.

### Co-workers, Subordinates and Students

Investigators proposing to recruit and select co-workers or students as research subjects must justify the necessity for including these individuals. The protocol must clearly articulate what steps will be taken to avoid the potential for coercion or undue influence when selecting subjects who are in a subordinate or peer relationship with the investigator.

## 9.12 IRB Review of Recruitment Methods and Participant Selection

Before approving research, the DDEAMC IRB evaluates whether the selection of research subjects is equitable within the confines of the study. The DDEAMC IRB examines the characteristics of the subject population outlined in the protocol and the procedures for identifying and recruiting subjects. The DDEAMC IRB will ensure persons are not excluded unnecessarily and appropriate protections are implemented. The DDEAMC IRB will pay close attention to the special problems raised by the selection of subjects from vulnerable populations, such as military recruits, military personnel in a training status, or coworkers.

The DDEAMC IRB also looks at the purposes of the research; specifically, whether the nature of the research requires or justifies using the proposed participant population and whether there is an intention for that population to benefit from the research. The setting in which the research will be conducted and the manner in which subjects will be recruited may also affect the equitable selection of subjects.

Studies with the potential to address issues relevant to both sexes must recruit both genders, and minority populations should be included in a study population wherever feasible. Researchers must justify the exclusion of any group of individuals. The DDEAMC IRB makes exceptions if there is adequate scientific justification for exclusion, such as when a condition predominates in one gender, or the focus of the research question is on a specific group.

The DDEAMC IRB will closely examine research that requests recruitment of subjects solely due to their easy availability, compromised position, or susceptibility to manipulation, such as students or MTF employees. The protocol should clearly articulate how the recruitment process will avoid the appearance of coercion when selecting subjects who are in a dependent relationship to the investigators.

The DDEAMC IRB will review recruitment materials to ensure they are informative, but not coercive or misleading, and do not imply an outcome or benefit for subjects unless it is also described in the study protocol and informed consent document. Additionally, an advertisement should not falsely imply or suggest that research is treatment. Overall, the advertisement should be limited to the information that prospective subjects need in order to determine their eligibility and whether they are interested.

The DDEAMC IRB will also review recruitment procedures and any payments or incentives provided to subjects/participants, with a view to determining whether the method of recruitment or amount of payment to subjects and the proposed method and timing of disbursement are coercive or present undue influence that may result in inequitable selection of subjects/participants.

The DDEAMC IRB will discuss and document appointing an ombudsman when DoD personnel (including civilians) are recruited in groups and has been determined to be greater than minimal risk. The ombudsman shall not be associated in any way to the research and shall be present during the recruitment in order to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman may also serve as the research monitor.

If the research project is no greater than minimal risk and the recruitment occurs in groups the IRB will determine if it is appropriate to require an ombudsman. This decision will be based on the human subject population, the consent process, and the recruitment strategy.

An Ombudsman will be appointed by the IRB in an appointment letter with responsibilities noted in the appointment letter.

## 9.13 Documentation of Approval Recruitment Process, Advertising Materials, and Payment

RRCO Responsibilities:

1. Document in the DDEAMC IRB meeting minutes that the protocol's recruitment process was reviewed and approved by the IRB.
    a. Of initial review, this process will be processed as part of the protocol approval if the recruitment materials are included in the original protocol packet; or by a specific vote: "I make a motion to approve recruitment of subjects using the telephone script dated xxx and the poster date xxx".
    b. After the protocol is approved by the DDEAMC IRB, the IRB Chair, or other designated IRB member, may review and approve advertisements by expedited procedures. However, if the IRB reviewer has doubts about the appropriateness or correctness of the information, the recruitment material should be reviewed at a convened meeting of the IRB.
2. Recruitment materials such as posters will be stamped with the DDEAMC IRB approval and expiration date.

## 9.14 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
9. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
10. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.

11. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
12. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
13. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
14. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
15. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
16. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 10: Informed Consent Process and Documentation

## 10.1 Purpose

The purpose of this policy is to provide guidance and direction about the process of research informed consent and the required documentation of that process in the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 10.2 Background

The process of research informed consent and the documentation of that process are the backbone of the relationship between the research subject and the research team. The IRB relies on the research team to treat the potential and recruited subjects with the highest level of respect as noted by their voluntary agreement to participate in research. This requirement is in place because the lines between treatment and research are often blurry. Subjects always have the choice to participate or to withdraw their participation at any time.

## 10.3 Definitions

**Assent** – A child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

**Children** – Persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In determining the capability of the child to give assent for research, the child's age (e.g., typically above 6 years), maturity and emotional state should be considered.

**Children's Assent Form (CAF)** – The document approved by the DDEAMC IRB for use to convey information to the child about the research study.

**Experimental Subject –** See "research involving a human being as an experimental subject."

**Guardian** – An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

**Informed Consent Form (ICF)** – The document approved by the DDEAMC IRB for use to convey information to the potential subject or their legally authorized representative about the research study.

**Legally Authorized Representative (LAR)** – An individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this policy and procedure**,** a legally authorized representative includes not only a person appointed as a health care agent under a Durable Power of Attorney for Health Care (DPAHC), a court appointed guardian of the person, but also next-of-kin in the following order of priority unless otherwise specified by applicable state law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

Legally authorized representatives are to be well informed regarding their roles and obligations to protect incompetent participants or persons with impaired decision making capacity. They must also be told their obligation is to try to determine what the prospective participant would do if competent, or if the prospective subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

**Parent** – A child's biological or adoptive parent.

**Permission** – The affirmative agreement of parent(s) or guardian for the participation of their child or ward in a research study.

**Research Involving Human Subject -** An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of 10 USC 980; it does not affect the application of part 219. This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at 32 CFR 219.101(b) and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

**Research involving a human being as an experimental subject** - An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the application of 10 USC 980; it does not affect the application of32 CFR 219. This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at 32 CFR 219.101(b), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

## 10.4 General Information about the Informed Consent Process

Informed consent is a continuous process that involves providing potential study subjects with sufficient information about the conduct of the research and potential benefits and risks so that the subject can make a reasoned and informed decision about whether to participate in the research study. This process begins at screening potential subjects and continues throughout the conduct of the study.

**Screening**
Per 32 CFR 219 (Common Rule) advance informed consent is required for all research procedures including screening. The Common Rule considers screening to be the onset of research; therefore, this cannot be performed without informed consent. However, the DDEAMC IRB can waive consent for the screening portion of the research (as long as the screening meets the 4 criteria for waiver IAW 32 CFR 219.116d – e.g., minimal risk, impracticable without waiver, etc.).

If the overall protocol is greater than minimal risk (GTMR) but the screening portion is minimal risk, a waiver can be granted for the screening portion. HIPAA authorization does not need to be waived at this point because the HIPAA rules allow for the review of protected health

information (PHI) by members of the covered entity for the purpose of seeking HIPAA authorization and therefore can be used in the recruitment of subjects (http://www.hhs.gov/hipaafaq/permitted/research/317.html).

The other option (vice waiver) is to have the investigator create a short "screening consent/HIPAA authorization" that would cover the screening portion of the research only. This is a good practice for studies in which the investigator will be retaining PII or PHI from all the potential subjects in the form of a screening log. After the screening consent is completed, and the subject is found eligible for the study, then the full consent should be obtained.

The FDA has guidance on this issue as well on the Guidance Information Website available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm116332.htm

The FDA guidance specifically talks about "procedures" performed solely for research purposes. It does not mention asking questions of a potential subject or reviewing a potential subject's information.

Risks must be explained in terms that the subject can understand and the process should empower subjects to make their own determination about risk. Human subjects must provide informed consent to participate in a research study and that process must take place prior to collecting any research related information from the subject.

1. Investigators and DDEAMC IRB members must remember that there is no such thing as “passive consent.” Consent is required unless formally waived and documentation of consent is required unless formally waived by the IRB. In addition, there is no such thing as a “secondary subject.” If an investigator obtains “identifiable private information” about a living individual, the individual is a human subject, regardless of who provided the information.
2. In accordance with Title 10 United States Code (USC) 980:
    a. Funds appropriated to the Department of Defense (DoD) may not be used for research involving a human being as an experimental subject unless:
        i. The informed consent of the subject is obtained in advance; or
        ii. In the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject.
    b. The Secretary of Defense may waive the prohibition in this section with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws.

**Protocol Description of Consent Process**

It is the responsibility of the investigator to ensure that the protocol includes the following description of the research informed consent process:

1. Identification of the individual(s) responsible for explaining the study, answering questions, and obtaining informed consent;

2. Information regarding the timing and location of the consent briefing;
3. Explanation of any efforts to be made to promote subject's understanding of the consent. Tools to assist the informed consent process include videos and demonstrations, photographs, sketches, and diagrams.
4. If applicable, address issues relevant to the mental capacity of the potential subject (e.g., altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation, or anesthesia, brain injury, stress life situations, or volunteer age);
5. If applicable, address issues related to the military unique human subject protections and how this will be addressed during the consent process;
6. How privacy for the potential subject will be managed and adequate time for decision-making will be provided, and whether or not the potential subject will be allowed to discuss the study with anyone before making a decision;
7. As informed consent is an ongoing process, consideration of the need for obtaining ongoing consent, or for re-assessing capacity over the course of a long-term study and describing any relevant procedures to assure continued consent;
8. If it is anticipated that subjects who do not speak the primary language of the host country will be enrolled into a trial, all documentation provided to subjects (ICF, information sheets, etc.) should be translated, with a copy provided to the DDEAMC IRB for review, to include a plan for ensuring that subjects questions can be addressed during the consent process and throughout the study duration.
9. A statement and explanation should be given if samples or data collected are to be used in future research. If the research is being conducted in an institution that is a covered entity, justification for HIPAA waiver requests should also be provided.

**Protection from Real or Perceived Coercion**

The issue of coercion, whether real or perceived, must be addressed by the investigator during the development of the research protocol as well as the during DDEAMC IRB review.

1. In considering the adequacy of the informed consent procedures, the DDEAMC IRB may monitor the process in order to reduce the possibility of coercion and undue influence. The IRB members, research monitor, and RRCO staff may be present during any subject recruitment and informed consent briefing.
2. The DDEAMC IRB will give special consideration to the recruitment process for DoD personnel to include the following IAW DoD Directive 3216.2, paragraph 4.4.4:
    a. During recruitment briefings to military personnel, an ombudsman, not connected in any way with the proposed research or the unit, shall be present to monitor that the voluntary nature of individual participation is adequately stressed and that the information provided about the research is adequate and accurate.
    b. Unit officers and noncommissioned officers (NCOs) may not influence the decisions of their subordinates for research that is greater than minimal risk (GTMR) and involves military personnel.

c. Individuals in the subject's chain of command may not be present at the time of research subject solicitation and consent. Peer pressure should also be considered and minimized, if possible.

d. When applicable, excluded individuals in the chain of command shall be afforded the opportunity to volunteer as research subjects in a separate recruitment.

**Types of Documentation of the Informed Consent Process**

The informed consent process will be documented by the use of a written informed consent form (ICF) approved by the DDEAMC IRB and signed by the subject or the subject's LAR, except as provided in 32 CFR 219.117(c). A copy of the signed ICF will be given to the person signing the form (32 CFR 219.117). The ICF may be either of the following [32 CFR 219.117(b)]:

1. A written consent form that includes the elements of informed consent required by 32 CFR 219.116
    a. This form may be read to the subject or the subject's legally authorized representative, but in any event,
    b. The investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or
2. Only the most recent DDEAMC IRB approved consent forms can be utilized by the research team. The IRB requires that if the consent form revisions have an impact on the risk to benefit ratio, then subject must be re-consented using the approved revised consent form. Sponsors may also have requirements regarding re-consent. The RRCO staff recommends that the research team members use the consent forms located in IRBNet to avoid any protocol deviations related to using an expired or incorrect informed consent form.
3. The short form written consent form as discussed below.

**Use of the Short Form Written Consent**

A short form written consent stating that the elements of informed consent required by 32 CFR 219.116 was presented orally to the subject or the subject's LAR.

a. The DDEAMC IRB must approve a written summary of what is to be said to the subject or the representative.

b. A witness is required to be present during the oral presentation.

c. Signatures are required as outlined below:
    i. Only the short form itself is to be signed by the subject or the LAR.
    ii. The witness must sign both the short form **and** a copy of the summary.
    iii. The investigator actually obtaining consent must sign a copy of the summary.

d. A copy of the summary and a copy of the short form will be given to the subject or the LAR.

**Informed Consent Form**

In order to protect against any perceived coercion to participate in a study, the DDEAMC IRB will assure that the informed consent form (ICF) explicitly states that subjects are voluntarily participating in a clinical investigation or research study (32 CFR 219.116).

1. The DDEAMC IRB will review the consent process as described by the investigator in the protocol, including the ICF and the process through which informed consent is obtained and documented from each subject. The DDEAMC IRB will focus on measures to improve subject understanding and voluntary decision-making during their review as well as consistency with the protocol.
2. The ICF must be recognized as the stand-alone document that serves as the physical reminder of the conversations and interactions between the subject and the research team. The ICF should be easy to read and understand while still complying with all applicable regulations.
3. The ICF must be free from any exculpatory language through which the subject or their representative is made or appears to waive any of their legal rights or releases, or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

**Formatting Requirements**

1. The ICF must be legible, with a font size equal to or larger than 12-point Times New Roman.
2. The form must be written at a reading level appropriate for the volunteers (i.e., 8$^{th}$ grade level for adults) and in the second person, that is, the subject is addressed as "you." The investigator(s) can be referred to in the first person, that is "I" or "we." However, the statement to be signed by the subject agreeing to take part in the study should be in the first person.
3. Pages will be numbered as "Page 1 of 3, 2 of 3, etc."
4. The investigator must provide a copy of the signed consent form to the subject or LAR.

**Required Elements per the Federal Regulations in the Informed Consent Form**

The following elements are required by federal regulations to be included in the ICF:

1. Identified research site(s);
2. Description of the research;
3. Clear explanation that the activity is research;
4. Brief statement of the purpose or objectives of the research;
5. Statement of sponsorship (i.e., DoD or Army organization);
6. Duration of participation;
7. Number of subjects expected in the study;
8. Description of procedures and time commitment, to include procedures that are for screening purposes or are experimental;

9. Specifics as to what is required of the subject;

10. Precautions to be observed by the subject;

11. Foreseeable risks, discomforts, and inconveniences; investigator knowledge of previous studies should be included; if applicable, statement that there may be unforeseeable risks;

12. A clear statement that the research involves the use of an investigational new drug or device, if applicable;

13. A clear statement of potential benefits, if any, without overstatement (compensation is not a benefit);

14. Statement of any alternative procedures if the study is a therapeutic study;

15. If subjects will receive payment, a description of the amount and timing of payment;

16. Description of possible costs to subjects because of study participation;

17. Description of compensation or medical care available for protocol-related injury (Refer to Chapter 1:Framework for additional guidance)

18. Extent to which confidentiality of records identifying the subject will be maintained, to include how identifying information will be stored and for how long, who will have access to the identifying data, disposition of the data, if specimens will be maintained and for how long. The following statement must be included in the consent form for all studies that enroll military personnel: "All data and medical information obtained about you, as an individual, will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised to subjects, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities."

19. A statement that representatives of the DDEAMC IRB, MRMC, CIRO, and AHRPO are eligible to review research records, in addition to the Food and Drug Administration and the sponsor (if applicable). If the research is subject to the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA), a HIPAA authorization is required, which must include the representatives of CIRO and AHRPO as one of the parties to whom protected health information may be disclosed;

20. A statement that participation is voluntary and that refusal to participate or withdrawal at any time will **not** involve any penalty or loss of benefits;

21. A statement describing the consequences of a subjects decision to withdraw, and procedures for the orderly end of a subject's participation and whether withdrawal of samples or data will be possible;

22. A statement informing the subject of anticipated circumstances under which the individual's participation may be terminated by the investigator, study sponsor, or others, without regard to the subject's consent such as the occurrence of an adverse reaction or injury, protocol violation, or early closure of the study;

23. A statement that the subject will be informed of any significant new findings;

24. Contact information for the principal investigator (PI), health care provider or research monitor, local lead or site investigator, and an individual for complaints or questions of volunteer rights;

25. A statement telling whether any samples will be collected and stored for use in future research, how long the samples will be retained, how they will be labeled (e.g., with initials, traceable code, new traceable code), and who will have access or where the samples will be kept; subjects should be given the option of participating in the study without donating their blood or tissue (if, applicable).

26. If the research involves the use of a subject's blood, tissue or body fluid for current or future genetic research, the consent document should, in addition to the information in item 25 above, explain:
    i. The types of information that could result from the genetic testing,
    ii. Potential risk if the genetic information is disclosed, either intentionally or inadvertently.
    iii. Whether the researchers intend on disclosing the results to the subjects,
    iv. Potential for commercial product development from the specimens obtained in the research protocol, and whether there is any plan to compensate them for the use of their samples.
    v. If unused portions of identified or identifiable samples might be shared with other researchers.
    vi. Options of tiered or multi-optioned informed consent: for example, the first option of consent could be for genetic aspects of the current study only, a second option could be storage of coded samples for goals broadly related to the current study, a third option could be permission to anonymize and save the specimens for any kind of future study.

27. If the research involves the use of a subject's blood, tissue or body fluid for current or future genetic research, the consent document should, in addition to the information in items 25 and 26 above and is conducted or supported by the Department of Health and Human Services (DHHS) (e.g., National Institutes of Health (NIH), National Cancer Institute (NCI) etc.), then the appropriate Genetic Information Nondiscrimination Act (GINA) language must be included exactly as stated below:

    *A new Federal law, called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:*

- *Health insurance companies and group health plans may not request your genetic information that we get from this research if the companies or the health plan administrator is not engaged in the research.*
- *Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.*
- *Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.*

*All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.*

*Be aware that this new Federal law does **not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance*

28. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable, if applicable to the study.

29. Signature of subject and date. NOTE: The subject is considered enrolled in the research at this point and all reportable events must begin.

30. Signature of witness and date (if a witness is required) as determined by the DDEAMC IRB.

**Children's Assent and Parental Permission**

When children are part of the research subject pool, children must provide an affirmative agreement to participate in research. Their agreement is noted as assent (45 CFR 46 Sub-Part D). Mere failure to object should not, absent affirmative agreement, be construed as assent. The parental permission for a child to participate in research must also be obtained. There are circumstances that will require different types of parental permission such as:

a. The permission of one parent

b. The permission of both parents

**General Features and Formatting Requirements for the Documentation of the Informed Consent Process with Children**

The Children's Assent form (CAF) is used to convey information about the research to the child. There are two age groups that are targeted: seven (7) to twelve (12) years old and thirteen (13) to seventeen (17) years old. There may be certain research studies where it may be appropriate for a sixteen (16) year old and older to sign the adult consent but these are determined on a case-by-case basis.

The following items are required for use in the Children's Assent:

1. First person is strongly preferred because it more accurately conveys to the child the nature of the assent process (the child is saying, "I agree"). The child may perceive an assent form written in the second person as a demand.
2. Language should be very simple and direct (no more than a second or third grade receptive vocabulary). This is true even for consents intended for teenagers.

3. A consent form does not substitute for an assent form, which should be simpler and shorter.
4. Keep sentence length short.

**Requirement for a Witness to the Informed Consent Process**

A witness is required to be present during the informed consent process for a potential subject if:

- The short form consent document is used as described earlier in this policy
- The individual is unable to read the consent document, or;
- If the individual is not given an opportunity to read the consent form, or;
- May be required if the potential subject is a member of a vulnerable population, even if the individual is thought able to read the consent form.

In this situation, the witness must have read the consent form or IRB-approved briefing summary and be present during the briefing. This witness then signs the consent form. If the subject signs the consent form at a later time, a different individual, unaffiliated with the study, can witness the signature.

## 10.5 Informed Consent Process Waiver or Alteration of the Documentation of the Informed Consent Process

**Preparatory to Research**

There is a method under HIPAA that allows the access of personally identifiable information for the purpose of "reviews preparatory to research." This method might serve as a part of the:

- Design of a research study,
- Feasibility assessment of conducting a study, or
- Assembling a database of individuals who indicate a willingness to be considered for participation in future research studies.

However, this method does not permit the:

- Collection of data for conducting actual research or
- Removal of information from a covered entity (CE).

The researcher must certify to the DCI in writing that:

1. The use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research as described earlier
2. The researcher will not remove any protected health information from the covered entity and
3. Representation that protected health information (PHI) for which access is sought is necessary for the research purpose IAW 45 CFR 164.512(i)(1)(ii).

See Chapter 6, Policy #12 for additional guidance and information.

**Waiver or Alteration of the Informed Consent Process**

Federal regulations (32 CFR 219.116(d)) do allow the DDEAMC IRB to approve a consent process which does not include, or which alters, some or all of the elements of informed consent

set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the subjects;
2. The waiver of alteration will not adversely affect the rights and welfare of the subjects;
3. The research could not be practicably carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

**Wavier of Informed Consent Documentation**
In order to approve a waiver of informed consent documentation (32 CFR 219.117), the IRB must find and document either of the following conditions:

a. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In these cases, each subject will be asked whether he/she wants documentation linking them with the research, and their wishes will govern; **or**

b. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

1. In cases in which a signed ICF is waived, the DDEAMC IRB may require the PI to provide the subjects with a written statement regarding the research. If children are subjects, an assent form may be necessary.
2. A waiver of informed consent does **not** absolve investigators of their responsibility to inform the study subjects of the nature and benefits of the project. The informed consent process must still occur, but the requirement to obtain a signed ICF is waived. For example, in the case of a mailed survey questionnaire, information that would normally be included in a consent form is included in a cover letter. In other cases, it may be possible to give the study subjects additional pertinent information about the study after participation.
3. The DDEAMC IRB's waiver of informed consent documentation authorization for a research study and its justification will be clearly documented in IRB minutes.
4. A minimal risk protocol approved by expedited review can also have the requirement to obtain informed consent waived by the IRB of record if it meets the criteria set forth in 32 CFR 219.116(d).
5. This waiver provision is not applicable to research governed by FDA regulations. The FDA does not permit waiver of informed consent documentation except in a clinical emergency or emergency research. The FDA regulations (21 CFR 56.109) are primarily associated with the waiver of informed consent documentation and state:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research:

- Presents no more than minimal risk of harm to subjects and
- Involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may for some, or all, subjects find that the requirements in paragraph 50.24 of this chapter for an exception from informed consent for emergency research are met. In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

**DoD Restrictions on Waiver of Informed Consent**

IAW DoDI 3216.02, November 8, 2012 which states:

> Sections 32 CFR 219.116(c) and (d) identify conditions where an IRB may waive informed consent for DoD-conducted and DoD-supported research involving human subjects. 10 USC 980 imposes limitations on waiving informed consent when using DoD appropriated funds. 10 USC 980 is applicable ONLY to DoD funded research involving a human being as an experimental subject (see definitions) The definition of research involving a human subject as an experimental subject is not the same as the definition of research involving human subjects. 10 USC 980 is not applicable to exempt research involving human subjects.

## 10.6 HIPAA Authorization

Under Health Insurance Portability and Accountability Act (HIPAA), the use or disclosure of Protected Health Information (PHI) for research purposes requires a signed Research Authorization Form from the research subject unless an exception applies. See Chapter 6, Policy #12 for additional guidance.

## 10.7 Translation for Non-English Speakers

Federal regulations (21CFR46 50.20) stipulate that any research involving non-English speaking subjects in any manner must have specific approval for their participation. Individuals may not be excluded from the study based on their inability to speak, read or write in English. The PI must also document how information will be communicated to these subjects in the protocol. This requirement extends to all written documents (e.g., informed consent, children's assent, subject diary cards, medication and dosing instructions, etc.). These documents must be written in the subject's native language to help ensure that the subject can fully understand the study.

The Translation Services covered under DDEAMC Memorandum Number 40-14 can assist with the translation needs. The document will be in a language that volunteers can understand. When the document is in a language other than English, the DDEAMC IRB requires a certificate of translation documenting that the foreign language version of the consent form is an accurate translation of the English form reviewed by the IRB. The certificate of translation should contain the following information about the individual translator:

a. Signature,

b. Name,

c. Address,

d. Phone number and, if available, fax number

e. Email address

## 10.8 Changes to the DDEAMC IRB Approved Informed Consent Process and Form

Changes to the research study or research team may require changes to the approved informed consent process and ICF. Please refer to the Amendments section of the HRPP for additional guidance.

An updated informed consent process or ICF will be requested at continuing review. Please refer to the Continuing Review section of the HRPP for additional guidance.

## 10.9 DCI Research Regulatory Compliance Office (RRCO) Staff and DDEAMC IRB Review of the Informed Consent Form:

The RRCO staff will perform an administrative review of the ICF to confirm that:

- All required elements are included and
- To check the reading grade level of the content.

**IRB Review of the Informed Consent Process and Forms:**

It is the responsibility of the DDEAMC IRB members to ensure that their review of the informed consent process as outlined in the protocol and the ICF(s) include:

1. Review by the DDEAMC IRB, IRB Chair, or designee of the ICF and protocol submitted by the PI and documented as part of the overall research review.
2. Determination of subjects as "experimental subjects" IAW 10 USC 98 to include
   A. Determination of DoD funding, either in part or wholly
   B. Determination of all subjects' ability to consent
   C. Availability of legally authorized representative to consent for those subjects who are unable to consent
   D. Determination of direct benefit to each subject in the study
3. The requirement that informed consent be obtained from the research subject in advance of the subject's participation in the research in accordance with 32 Code of Federal Regulations (CFR) 219.116.
4. Determination that informed consent will be appropriately documented, unless documentation is waived under the Common Rule in order to approve research.
5. Ensure that the research protocol and ICF adequately address saving tissues or body fluids for future use where appropriate.
6. Consideration of the timing and setting of the initial consent process to assure the circumstances minimize the possibility of coercion or undue influence and provide the individual with sufficient opportunity to consider whether or not to participate.

7. Evaluation of the consent process at continuing review and when reviewing modifications to the research to assure that the informed consent process remains adequate for the protection of the rights and welfare of the subjects.

## 10.10 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. 22 October 2004, Memorandum Subject: Applicability of 10 U.S.C. 980 to Minimal Risk Research and Research Not Benefitting the Subject
15. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 11: Collaboration, Reliance and IRB Submission/Review

## 11.1 Purpose

The purpose of this policy is to delineate DDEAMC requirements and the assignment of responsibilities when DDEAMC is conducting non-exempt research involving human subjects in collaboration with another investigator or institution IAW DoDI 3216.02, Enc 3.1.c(4) and Enc 3.3.a(7) and (8). Three types of collaborations will be discussed:

1. DDEAMC Investigator is engaged in the conduct of a single, unified protocol that is engaged in by two or more Assured institutions.

2. DDEAMC Investigator is engaged in a multi-site study, where the core-protocol is conducted at the research sites by a Site Investigators, under the oversight of a Lead Investigator.

3. A Non-DDEAMC investigator, who is not associated with an Assured institution, is engaged in the conduct of a single, unified protocol in collaboration with DDEAMC.

## 11.2 Policy

DDEAMC investigators may only be engaged in non-exempt research involving human subjects that is conducted by institutions which hold a Federal assurance of compliance acceptable to the funding institution. Each such protocol must have (a) scientific merit review which has been considered by the institutional review board (IRB), (b) IRB review and approval before the research is undertaken, and (c) when required, review by a properly constituted Privacy Board IAW DoD 6025.18-R, C7.9. The DoD has authorized the use of Institutional Agreements to (1) reduce the duplication of IRB reviews of the same project and (2) facilitate the clear definition of roles, responsibilities, and expectations in collaborative research efforts.

## 11.3 Definition

"Collaboration", utilized in DoDI 3216.02, is not defined. For the purpose of the policy, "collaboration" means the same as "cooperative research projects" as defined by 32 CFR 219.114. "Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort." The underlying premise here is that two or more institutions are engaged in non-exempt research involving human subjects.

## 11.4 Assurances

Any institution engaged in non-exempt human subjects research that is conducted or supported by the DoD shall have a Federal assurance consistent with 32 CFR 219, and acceptable to the funding agency. A DoD-institution engaged in non-exempt human subjects research shall have a DoD assurance of compliance and, when the research is funded by HHS, also have a HHS assurance of compliance. DoDI 3216.02, Enc 3.2.a.

For the purpose of this Chapter, only institutions that hold a Federal assurance acceptable to DoD will be considered for the purpose of engaging in collaborations with DDEAMC. A Non-DDEAMC investigator, who is not associated with an Assured institution, may also be considered for the purpose of engaging in the conduct of a single, unified protocol in collaboration with DDEAMC. In the case of the non-DDEAMC investigator, the DDEAMC assurance of compliance may be extended to cover the non-DDEAMC investigator under an Individual Investigator Agreement (see section 11.8.2below). DoDI 3216.02, Enc 3.2.a(2)(a)

An institution whose conduct in the collaboration does not rise to the level of engaging the institution in non-exempt research involving human subjects, is not required to have a Federal assurance, and is not covered by this Chapter. Collaborative activities that do not rise to the level of engagement include following:

(1) Specific tasks that do not involve research involving human subjects; or

(2) Specific tasks that do not include the collection or handling or identifiable data or specimens. Research in which the human subjects' data or specimens are coded and the institution is prevented from having access to the code are considered non-identifiable for the purpose of this subparagraph. DoDI 3216.02, Enc 3.2.b(3).

### 11.5 Minimizing Scientific Review

Scientific review is required for non-exempt research involving human subjects. This review must considered during the IRB review process, whether or not the IRB that is conducting the review is a DoD-IRB under DoDI3216.02, Enc 3.3.a(7), See DoDI3216.02, Enc 3.3.a(2) and Enc 3.3.a(8).

### 11.6 Minimizing IRB Review

Assured institutions must have an identified primary Institutional Review Board (IRB). 32 CFR 219.103(b)(2). The IRB may be internal or external to the institution.

(1) DoD-Institutions operating under a DoD Assurance must use the services of an IRB whose membership conforms to the unique requirements of a DoD-IRB as established by DoDI 3216.02, Enc 3.3.a(7). As such, when DDEAMC is engaged in non-exempt human subject research in collaboration with another DoD-institution holding a DoD assurance, the DoD-institutions shall establish a written agreement for minimizing the number of IRB reviews.

(2) An exception exists, which allows DDEAMC, and other DoD-institutions, to rely upon the IRB of a collaborating non-DoD institution when these conditions are met:

(a) The DoD Component determines the collaborating non-DoD institution has an appropriate Federal assurance.

(b) The involvement of DoD personnel in the conduct of the research involving human subjects is secondary to that of the non-DoD institution.

(c) The DoD institution, the non-DoD institution, and the non-DoD institution's IRB have a written agreement defining the responsibilities and authorities of each organization in complying with the terms of the Federal assurances and this Instruction (i.e., have an Institutional Agreement for IRB Review or similar agreement). The DoD Component

shall approve the terms of the agreement prior to the DoD institution's engagement in the research involving human subjects.

(d) The DoD Component (through AHRPO) must conduct an appropriate administrative review of the research involving human subjects to ensure it is in compliance with DoD policies and procedures prior to the DoD institution's engagement in the research. See DoDI 3216.02, Enc 3.3.a(8)

**11.7**

### 11.7.1 Single, Unified Protocol

When a DDEAMC Investigator is engaged in the conduct of a single, unified protocol that is engaged in by two or more Assured institutions, the following must be identified before any agreement as to the distribution of responsibilities can be negotiated:

(1) All research personnel, including their research roles, responsibilities, and institutional affiliations

(2) All engaged institutions

(3) All Federal assurances that cover each engaged institution

(4) The Lead Investigator

(5) Resources that each institution must make available for the research (including impact statements)

(6) How independent scientific review will be provided

(7) The Lead IRB (usually, but not always, associated with the Lead Investigator's institution).

(8) The applicable policies and procedures for IRB/Privacy Board submission, review, processing, and notification of the institutions and the investigators involved (throughout the life-cycle of the research).

(9) The applicable policies and procedures for receiving, investigating, and resolving complaints, allegations or reports of unanticipated problems involving risks to subjects or others or noncompliance.

(10) The responsibilities and authorities of each engaged institution in complying with the terms of their Federal assurance(s) and applicable Federal regulations (i.e. DoDI 3216.02, DoD 6026.28-R, etc.)

(10) How the engaged institutions will communicate with each other and the investigators.

### 11.7.2 Multi-site Protocol

When a DDEAMC Investigator is engaged in a multi-site study, where the core-protocol is conducted at the research sites by Site Investigators, under the oversight of a Lead Investigator, the following must be determined before any agreement as to the distribution of responsibilities can be negotiated:

(1) The elements and scope of the core protocol

(2) The elements and scope of the site specific addendums that must be in place for each research site

(3) Resources that the Lead institution must make available for the research

(4) Resources that each research site must make available for the research (including impact statements)

(5) The Lead Investigator and key research personnel (including their roles and responsibilities) supporting the core protocol

(6) The roles and responsibilities to be carried out by the site investigator and site research staff (including their roles and responsibilities)

(7) The lines of communication between the Lead Investigator and the Site Investigator

(8) The lines of communication between the Lead Investigator and any regulatory authorities or oversight bodies

(9) The lines of communication between the site investigator and any regulatory authorities or oversight bodies

(10) All institutions to be engaged initially

(11) All Federal assurances that cover the institutions, which are initially engaged

(12) How independent scientific review will be provided

(13) The Lead IRB/Privacy Board (usually, but not always, associated with the Lead Investigator's institution).

(14) The applicable policies and procedures for IRB/Privacy Board submission, review, processing, and notification of the institutions and the investigators involved (throughout the life-cycle of the research).

(14) The applicable policies and procedures for receiving, investigating, and resolving complaints, allegations or reports of unanticipated problems involving risks to subjects or others or noncompliance.

(15) The responsibilities and authorities of each engaged institution in complying with the terms of their Federal assurance(s) and applicable Federal regulations (i.e. DoDI 3216.02, DoD 6026.28-R, etc.)

(16) How the engaged institutions will communicate with each other and the investigators.

### 11.7.3 Non-DDEAMC investigator without an Assured Institutional Affiliation

When a non-DDEAMC investigator who is not associated with an Assured institution, is engaged in the conduct of a single, unified protocol in collaboration with DDEAMC, the following must be identified before any agreement as to the distribution of responsibilities can be negotiated:

(1) All research personnel, including their research roles, responsibilities, and institutional affiliations

(2) All engaged institutions (including identification of the institution (if any) with which the Non-DDEAMC, non-DoD assured investigator is associated)

(3) All Federal assurances that cover each engaged institution

(4) The resources that will be provided for the research, and by whom

(5) The Lead Investigator

(6) How independent scientific review will be provided

(7) The Lead IRB/Privacy Board (usually, but not always, associated with the Lead Investigator's institution).

(8) The applicable policies and procedures for IRB/Privacy Board submission, review, processing, and notification of the institutions and the investigators involved

(9) The applicable policies and procedures for receiving, investigating, and resolving complaints, allegations or reports of unanticipated problems involving risks to subjects or others or noncompliance.

(10) The lines of communication between DDEAMC and the non-DDEAMC investigator

(11) The lines of communication between DDEAMC and the non-DDEAMC investigator's institution

## 11.8 Agreements

### 11.8.1 Institutional Agreements for IRB Review

DDEAMC may enter into an Institutional Agreement for IRB Review (IAIR) with any institution holding a Federal assurance approved by the funding entity. DDEAMC may expand the traditional IAIR to also engage or provide the services of a Privacy Board IAW DoD 6025.18-R, C7.9. However, DDEAMC may only rely upon the services of a non-DoD institution's IRB in the review of non-exempt research involving human subjects when the requirements of section 11.6.2 above have been met. When relying upon another institution's IRB, the written agreement must define the responsibilities and authorities of each organization and how these will be carried out.

### 11.8.2 Individual Investigator Agreement

When a non-DDEAMC investigator is not affiliated with an institution, or if that individual is affiliated with an institution that does not have a Federal assurance, DDEAMC may enter into an Individual Investigator Agreement (IIA) to associate the non-DDEAMC investigator with DDEAMC (an institution holding a DoD assurance), and thus fulfill the requirement of conducting non-exempt research involving humans subjects under an approved Federal assurance. Through the IIA, the non-DDEAMC investigator is bound by the terms of DDEAMC's assurance, HRPP Plan, and oversight. If the non-DDEAMC investigator maintains an institutional affiliation, that institution must be aware of the IIA.

The extension of DDEAMC's Assurances to a non-DDEAMC investigator (through an IIA) will only be approved when the following conditions have been satisfied:

(1) An investigator covered directly under DDEAMC's Assurances will appropriately supervises the research activities to be performed by the non-DDEAMC investigator.

(2) The following documents are made available to the non-DDEAMC investigator:

(3) The Belmont Report: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research or other internationally recognized equivalent*;

(4) The DoDI 3216.02, AR 70-25, AR 40-7, and 32 CFR 219 (The Common Rule)

(5) DDEAMC policies and procedures for the protection of human participants.

(6) The non-DDEAMC investigator understands and accepts his/her responsibility

(a) to comply with the standards and requirements established through the referenced documents and

(b) to protect the rights and welfare of human participants involved in the covered research.

(7) The non-DDEAMC investigator agrees to complete all DDEAMC-required educational training, to submit all relevant credentials, and receive any required privileges prior to initiating engaging in the research.

### 11.8.3 Filing and Maintenance of Agreements

DDEAMC will maintain agreements made under this chapter for at least three-years after the termination of the research. It will also provide copies of these agreements to the Army Human Research Protections Office (AHRPO).

## 11.9 Funding Agreements

### 11.9.1 USAMRMC Funding, Cooperative Agreement

When USAMRMC Defense Health Program (DHP) 6 funding is directly supporting a collaborative research enterprise which would engage DDEAMC in non-exempt human subject research, the resources to be provided to DDEAMC, and the responsibilities to be assumed by DDEAMC, must be outlined within the statement of work, which accompanies the Cooperative Agreement entered into between the grantor (USAMRMC) and the grantee (the direct recipient of the USAMRMC funding). A statement of work which does not identify DDEAMC as a beneficiary of the Cooperative Agreement will need to be either (a) amended or (b) rescinded and reissued before DDEAMC can enter into a collaborative research relationship with the grantee.

### 11.9.2 Extramural Funding, Cooperative Research and Development Agreement (CRADA)

In its simplest form, a CRADA is a joint technology transfer research agreement between a non-federal institution and the Clinical Investigations Regulatory Office (CIRO) serving as the Federal Laboratory, on behalf of DDEAMC. The non-federal institution may provide funds, personnel, services, facilities, equipment, intellectual property or other resources under DoDI 6000.08 and AR 70-57 for the conduct of specific research or development efforts that are consistent with DDEAMC's missions. Two tools are frequently encountered. One, a Master CRADA, supporting multiple projects which are presented individually as " statement of work" documents. Two, a Simple CRADA, which supports a single project and a single statement of work. A statement of work which does not identify DDEAMC as a beneficiary of the CRADA,

and which would engage DDEAMC in non-exempt human subject research, will not be accepted by DDEAMC.

### 11.9.3 Other Funding Mechanisms

A wide variety of other funding mechanisms exist to support DDEAMC's engagement in non-exempt human subject research, to include intra-agency agreemenst to document processes and then MIPR or FAD transfers. While not all are discussed within the HRPP, all are subject to the HRPP and do not replace IIAs, IAIRs, or DDEAMC IRB Review.

Adequate time must be allowed for the development and approval of collaborative research agreements that would engage DDEAMC in the conduct of non-exempt human subject research. Investigators who intend to participate in collaborative research should seek guidance from the DDEAMC Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO) early in the discussions about collaborative research.

**Additional information on Research Funding may be found at INSERT**

## 11.10 DDEAMC Institutional Responsibilities in Supporting Collaborative Research

### 11.10.1 DDEAMC PI

(1) Contact the DDEAMC Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO) to discuss the details of a collaborative relationship under development

(2) Work with the collaborative sites to identify the information required to support collaboration and an agreement

(3) Communicate with the DDEAMC DCI RRCO in a timely manner regarding any proposed changes to the collaboration

(4) Submit all documents as required under the agreement for scientific and IRB review

(5) Report any noncompliance or unanticipated problems involving risks to submects or others immediately to the the DDEAMC DCI RRCO

### 11.10.2The DDEAMC Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO) staff responsibilities are:

(1) Identify all research personnel that will be engaged in human subject research

(2) Identify all institutions that will be engaged in human subject research, and confirm that all institutions have an appropriate Federal assurance

(3) Identify the resources that DDEAMC will be providing for the research (including letters of support and impact statements); and the resources required that non-DDEAMC institutions or individuals will be providing. Confirm that resources will be available for the successful conduct of research.

(4) Contact the HPA at each participating assured institution to negotiate roles and responsibilities.

(5) Draft a formal written agreement that defines parties to the agreement, their responsibilities, and communication pathways. Each agreement must be customized based upon the specific requirements of the protocol. Ensure that the agreement is properly vetted within DDEAMC and is acceptable to the other parties who have an interest in the agreement before presenting the agreement for signature.

(5) Forward the written agreement to the DDEAMC Commander for signature and to the appropriate official(s) of the other institution(s) prior to submitting the research protocol to the IRB. Scientific review may occur in advance.

(6) Serve as the primary conduit for communication between the DDEAMC HPA and the HPA at the collaborating institutions.

(7) Report immediately to the DDEAMC HPA any issues, concerns, challenges, allegations, reportable events or other unanticipated problems as they arise in this collaboration.

**11.10.3 The DDEAMC Commander responsibilities are:**

(1) Having the authority to commit organization resources.
(2) Sign the formal written agreement that defines mutual responsibilities.
(3) Enforce the terms of the agreememnt

**11.10.4 IRBs of Record responsibilities are:**

- Review a submitted protocol for the protection of human research subjects under 32 CFR 219, DoDI 3216.02; and, as appropriate, serve as the Privacy Board under DoD 6026.18-R..
- Report to each institution that is engaged in the research and relying upon the review of this IRB its findings, determinations and actions in a timely manner.
- Communicate with the Commander for approval status.

## 11.11 IRB and Privacy Board Review Arrangements

The IRB listed on the Assurance of each collaborating institution has the responsibility for the review and oversight of research on behalf of the assured institution. Unless other formal arrangements are in place, an IRB of record from each institution engaged in the research must review and approve the protocol; therefore, there can be more than one IRB of record for a research protocol.

### 11.11.1 Review by 2 or More IRBs Independently

The default procedure is to have the protocol (and any changes, renewals, and reports of noncompliance) reviewed by both (or all) institutions' IRBs. DDEAMC guidelines allow submitting the protocol to either IRB first, or to both simultaneously (other institutions may

have other policies). However, it's generally recommended that the protocol be submitted first to the IRB of the institution that is most heavily involved in the research. This IRB would then be designated as the Lead IRB. When the requirements of the Lead IRB have been satisfied, subsequent reviews by other IRBs will generally go more smoothly. When a second IRB's review follows that of the Lead IRB, include in the submission package to the second IRB the approval letter from the Lead IRB.

,In the event the second reviewing IRB requires modifications to the protocol, these must be submitted back to the Lead IRB as an amendment. The research may not begin until all IRBs have approved the same protocol and study documents. The exception to this rule is that sites may have their own recruitment and consent processes which need only to be reviewed and approved by that site's IRB. However, the Lead Investigator and Lead IRB must be aware of this situation and concur.

### 11.11.2 Review by 2 or More IRBs Jointly

Collaborative institutions may agree to an exchange of information, such as IRB meeting minutes, reviewer checklists, and documentation of IRB review and approval via a web-enabled software system, if applicable, to complete their individual reviews. Such arrangements must be:

(a) In writing,

(b) Approved and signed by the DDEAMC Commander (or designee), and

### 11.11.3 Review by a Single IRB of Record

An IRB is considered the "IRB of Record" when it assumes IRB responsibilities for the review and oversight of a study. Utilizing Institutional Agreements for IRB Review (IAIRs), multiple institutions engaged in non-exempt research involving human subjects can minimize the number of IRB reviews required, and may even rely on a single IRB to conduct the review and oversight on behalf of each of the engaged institutions. The reviewing IRB would be known as the IRB of Record for that study, and would be responsible for communicating its reviews, findings, determinations, and outcomes to each collaborating institution on whose behalf the IRB is providing service.

In selecting a single IRB of Record, institutions must give careful consideration to all circumstances surrounding the project. DDEAMC IRB will not serve as a single IRB of Record in for collaborative research if DDEAMC cannot exercise adequate oversight of the research activities.

DDEAMC's RRCO coordinates the negotiation and approval of IAIR. In the event that a single Lead IRB is engaged, each institution relying on that IRB continues to remain responsible for the ethical and regulatory compliance of the conduct of the study at their location, and maintains copies of the IAIR for the required record retention period.

### 11.11 .4 Institutional Agreement for Institutional Review Board (IRB) Review (IAIR) Process in the Web-Enabled Software System for Multi-site Research

The Institutional Agreement for Institutional Review Board (IRB) Review (IAIR) is used when an institution will be engaged in human subject research and will use an Institutional Review Board (IRB) that is not organizationally or legally part of the institution. This Agreement will help ensure that the engaged institution with the federal assurance and the IRB providing the review and approval of the research IAW 32 CFR 219 and DoD Directive 3216.02 have documented the responsibilities of both parties to this agreement. Contact the DCI RRCO staff for additional guidance on this process.

**Lead Investigator Processes**

There are roughly four scenarios based processes that may be appropriate. They are:

1. Unified Protocol, DDEAMC person is NOT the Lead investigator

2. Unified Protocol, DDEAMC person IS the Lead investigator

3. Multi-site trial, DDEAMC person IS the Lead investigator, responsible for core protocol and all site specific addendums

4. Multi-site trial, DDEAMC person is NOT the Lead investigator, executes the core protocol, submits site specific addendums through the Lead investigator

Each of the four scenarios requires a slightly different process and these are outlined below for your convenience. These may change as new technology or processes become available.

Scenario 1 - Unified Protocol, DDEAMC person is NOT the Lead investigator

The Lead Investigator over the project submits the project via the web-enabled software system to the IRB of record with the IAIR document included in the submission process. In addition, the primary site PI will utilize the multi-site share option to create a new project for assignment to a local PI. This will link the sites and provide access to documents at all sites. The local PI then submits the project for review to the DDEAMC IRB for site specific responsibilities only, to include the following documents:

- Site specific protocol addendum that includes information on site specific requirements
- Informed consent/assent forms, as applicable
- HIPAA Authorization(s), as applicable
- Impact statements, as applicable

The following documents should be submitted for each research team member at DDEAMC or its covered MTFs:

- CITI
- CV
- Conflict of interest form

**DDEAMC DCI RRCO staff responsibilities**

After conducting an administrative review, the Protocol Coordinator shares the submitted package with the DDEAMC IRB Chair who reviews the package and forwards for IO

approval of the IAIR. Upon receipt of the DDEAMC IRB and IO approved IAIR, the Protocol Coordinator submits this document and the approved package to the IRB of record for the primary site. The IRB of record documents their approval and release of start date so that the DDEAMC IRB can release the start notice for the local site.

Scenario 2 - Unified Protocol, DDEAMC person IS the Lead investigator

The DDEAMC Lead Investigator over the project submits the project via the web-enabled software system to the IRB of record with the IAIR document included in the submission process. In addition, the primary site PI will utilize the multi-site share option to create a new project for assignment to a local PI at other sites. This will link the sites and provide access to documents at all sites. The DDEAMC Lead PI then submits the project for review to the DDEAMC IRB to include the documents noted in the Quick Glance Investigator Guide.

- Protocol
- Site specific protocol addendum that includes information on site specific requirements
- Informed consent/assent forms, as applicable
- HIPAA Authorization(s), as applicable
- Impact statements, as applicable
- Other documents as applicable based on the type of research

A conflict of interest form must be completed by each member of the research team.

The following documents should be submitted for each research team member at DDEAMC or its covered MTFs in the individual;'s User Profile and linked to the project:

- CITI
- CV

**DDEAMC DCI RRCO staff responsibilities**

After conducting an administrative review, the Protocol Coordinator shares the submitted package with the DDEAMC HPA who assigns a SR and IRB reviewer. Upon receipt of the DDEAMC IRB and IO approved IAIR, the Protocol Coordinator submits this document and the approved package to the IRB for their review and approval. The IRB of record documents their approval and release of start date.

Scenario 3 - Multi-site trial, DDEAMC person IS the Lead investigator, responsible for core protocol and all site specific addendums

The research protocol must define the specific roles and responsibilities of each collaborative investigator, the performance sites of all research-related activities, and the support to be provided by each institution. The protocol should briefly describe who is primarily responsible for recruitment of subjects, obtaining informed consent, conduct of specific research procedures, and maintenance of study records. All collaborators must ensure compliance with all relevant human subject protection regulations at their sites.

DDEAMC research studies involving a collaborating institution must include a statement in the consent form indicating the existence of the collaborative relationship. Use of a single,

consolidated informed consent document for such studies is strongly encouraged. All required DoD or Army clauses and any required boilerplate text of the collaborating institutions should be incorporated into the consent document prior to IRB review. It is important that all researchers work closely together to develop a protocol and consent form that will be acceptable to all reviewing IRBs.

Army regulations require review of protocols and test plans for scientific merit before submission to the IRB. The institution with the reviewing IRB or performing the research will conduct or verify that the research has been approved by an independent scientific review process. Collaborative research funded by the USAMRMC requires Human Research Protection Office (HRPO) before initiation of the research.

If review of a research study is deferred to another IRB that is using the web-enabled software system, the submission package to that IRB should be made available to the members of the DCI RRCO at DDEAMC to include all associated protocols and consent documents required at collaborating institutions. A protocol file will be maintained at DDEAMC. The DDEAMC lead investigator will verify that the DDEAMC DCI RRCO staff has received notification of any amendments or changes, reports of adverse events, and unanticipated problems and deviations submitted to the non-DDEAMC IRB, as well as all annual reports or continuing review reports, and certifications of annual IRB review and approval. DDEAMC will continue to track the protocol as an active study protocol. Thus, the DDEAMC Assurance covered lead investigator must submit a final report to the IRB to close the protocol as outlined in the section on IRB Policies and Procedures.

The DDEAMC Lead Investigator over the project submits the project via the web-enabled software system to the IRB of record with the IAIR document included in the submission process. In addition, the primary site PI will utilize the multi-site share option to create a new project for assignment to a local PI at other sites. This will link the sites and provide access to documents at all sites. The DDEAMC Lead PI then submits the project for review to the DDEAMC IRB to include the documents noted in the Quick Glance Investigator Guide.

- Protocol
- Site specific protocol addendum that includes information on site specific requirements
- Informed consent/assent forms, as applicable
- HIPAA Authorization(s), as applicable
- Impact statements, as applicable
- Other documents as applicable based on the type of research

A conflict of interest form must be completed by each member of the research team.

The following documents should be submitted for each research team member at DDEAMC or its covered MTFs in the individual;'s User Profile and linked to the project:

- CITI
- CV

**DDEAMC DCI RRCO staff responsibilities**

After conducting an administrative review, the Protocol Coordinator shares the submitted package with the DDEAMC HPA who assigns a SR and IRB reviewer. Upon receipt of the DDEAMC IRB and IO approved IAIR, the Protocol Coordinator submits this document and the approved package to the IRB for their review and approval. The IRB of record documents their approval and release of start date.

Scenario 4 - Multi-site trial, DDEAMC person is NOT the Lead investigator, executes the core protocol, submits site specific addendums through the Lead investigator

The Lead Investigator over the project submits the project via the web-enabled software system to the IRB of record with the IAIR document included in the submission process. In addition, the primary site PI will utilize the multi-site share option to create a new project for assignment to a local PI. This will link the sites and provide access to documents at all sites. The local PI then submits the project for review to the DDEAMC IRB for site specific responsibilities only, to include the following documents:

- Site specific protocol addendum that includes information on site specific requirements
- Informed consent/assent forms, as applicable
- HIPAA Authorization(s), as applicable
- Impact statements, as applicable

The following documents should be submitted for each research team member at DDEAMC or its covered MTFs:

- CITI
- CV
- Conflict of interest form

**DDEAMC DCI RRCO staff responsibilities**

After conducting an administrative review, the Protocol Coordinator shares the submitted package with the DDEAMC IRB Chair who reviews the package and forwards for IO approval of the IAIR. Upon receipt of the DDEAMC IRB and IO approved IAIR, the Protocol Coordinator submits this document and the approved package to the IRB of record for the primary site. The IRB of record documents their approval and release of start date so that the DDEAMC IRB can release the start notice for the local site.

## 11.12 Situation Guidance

Investigators from other federal agencies physically located at Fort Gordon but not affiliated with DDEAMC who conduct research that does not involve DDEAMC staff (military, civilian or contractors) as the primary research subject pool must be reviewed under their appropriate IRB.

The information below is based on current scenarios and guidance from CIRO although it may change based on TMA:

- National Security Administration (NSA) personnel must submit their protocols to U.S. Army Medical Research and Materiel Command (USAMRMC) IRB. If a NSA investigator would like to develop a research study that will involve DDEAMC staff, then the investigator should contact MRMC IRB for additional guidance.
- If a DDEAMC staff member would like to use data from a DoD database then the investigator should contact PASBA with procedures for requesting access to electronic medical records outside the covered MTF for research purposes.
- If the researcher is planning to use AHLTA medical originating outside of the Army, then the PI will need to get authorization from the other DOD branch. Listed below are the Navy and Air Force POCs.
    - Navy

      Manager Bureau of Medicine and Surgery (M3/5 HCS3) Building 1, Room 1001 2300 E Street NW Washington, DC 20372-5000 Phone: 202-762-3162
        - DSN: 762-3162
        - FAX: 202-762-3743
    - Air Force

      Division, Office of the Surgeon General, AFMOA/SG3SA, 485 Quentin Roosevelt Road, Bldg 171, San Antonio, TX 78226-1865
        - DSN 945-1185: COM (210) 925-1185
        - FAX (210) 925-1188

### 11.13 References

The following references are provided for informational purposes:

1. Department of Defense Instruction 3216.02. Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research. November 2011.
2. 32 Code of Federal Regulations (CFR) 219, Protection of Human Subjects in DoD Supported Research, dated 1 January 2009.
3. Office of Human Research Protections (OHRP) DRAFT - OHRP Guidance on Engagement of Institutions in Human Subjects Research, 16 October 2008.
4. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 12: Reportable Events - Unanticipated Problems, Serious Adverse Events and Deviations

## 12.1 Purpose

The purpose of this policy is to provide information about the reportable events (unanticipated problems, serious adverse events and major deviations) that the Principal Investigator (PI) is responsible for reporting to the Dwight D. Eisenhower Army Medical Center (DDEAMC) Institutional Review Board (IRB) as part of the Human Research Protection Program (HRPP).

## 12.2 Background

Federal regulations require that unanticipated problems involving risk to subjects or others, which includes a subset of adverse events, be promptly reported to the IRB, appropriate institutional officials, and any supporting department or agency head [32 CFR.103 (b)(5)]. Additionally, 32 CFR 219.11 states, "IRBs shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or has been associated with unexpected serious harm to subjects." To exercise this important authority in a timely manner, IRBs must be informed promptly of those adverse events that are serious, unexpected, and related (or possibly related) to participation in the research.

All investigators conducting non-exempt human research who rely on the DDEAMC IRB for review and approval of their research are subject to the policies and procedures outlined below.

## 12.3 Definitions

**Adverse Event -** Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

**Deviation -** Any change or departure from the research activities outlined in the approved protocol, that is *under a researcher's control* and that has not been reviewed by the IRB and approved by the Institutional Official/Commander prior to its initiation or implementation.

**Expected Adverse Event** - Any adverse event occurring in one or more subjects participating in a research protocol with the nature, severity, or frequency of which is consistent with these issues:

1. The known risks or side effects of the research procedures or interventions;
2. The expected natural progression of subjects' underlying diseases, disorders, and conditions;
3. Subjects' predisposing risk factor profiles for the adverse events.

**Major Deviation -** Adversely affects or may affect the rights, safety, or well-being of subjects; the integrity of the study data; or affects a subject's willingness to continue study participation. These may pose an immediate hazard to a subject.

**Minor Deviation -** Does not substantially impact the rights, safety, or well-being of research

subjects; does not affect the value of the data collected; does not result from willful or knowing misconduct on the part of the investigators or study staff; does not violate any ethical principles.

**Other Individuals -** Research personnel, subjects' family members are included in the concept of unanticipated problems.

**Possibly Related** - Reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

**Serious Adverse Event -** Any adverse event that results in death, is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, or based upon appropriate medical judgment, may jeopardize the patient or subject, or may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. A serious adverse event may be an adverse event that escalated.

**Unanticipated Problem (UP) -** Any incident, experience, or outcome that is unanticipated or unexpected; suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized; and was related, or possibly related, to participation in the research.

**Unexpected Adverse Event -** Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; **or**

2. The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

## 12.4 Reportable Events

Reportable events require prompt reporting to the DDEAMC IRB as outlined in this chapter as well as in Chapter 6 Policy #10 Deadlines for Submission to the IRB by the PI. The events may be separate or inter-related depending on each event. The types of reportable events are listed below:

- Unanticipated problem involving risks to subjects or others (UPIRSO)
- Adverse events (AE), unexpected **and** related for drugs or devices
- Serious adverse events (SAE)
- Protocol deviations/protocol violations
- Possible serious or continuing non-compliance

## 12.5 Unanticipated Problem (UP) Involving Risks to Subjects or Others (UPIRSO)

The term, Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO), is not defined in regulations. The AHRPO has stated that they are accepting DDHS OHRPs guidance that UPIRSOs include any incident, experience or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or other individuals (e.g., research personnel, subjects' family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The actual event that triggers consideration as a UPIRSO may be a data breach or other adverse event that has an impact on the risks as described in the Chapter 8 Research Risks and Benefits.

UPIRSOs often warrant consideration of substantive changes in research protocol or informed consent. These will usually require an amendment to the protocol. Examples:

- Changes to eliminate apparent immediate hazards to subjects
- Modifications of inclusion or exclusion criteria to mitigate newly identified risks
- Additional monitoring procedures
- Suspension of enrollment
- Suspension of research procedures for enrolled subjects
- Modification of informed consent forms
- Notification of previously enrolled subjects regarding newly recognized risks
- UPIRSO can place subjects or others at increased *risk* of harm.

Some, but not all, UPIRSOs are also adverse events or the result of noncompliance. These topics are discussed later in this chapter.

Examples of unanticipated problems include, but are not limited to:

- More frequent or severe side effects than were anticipated, as described in the protocol and consent form;
- Experiences or side effects by one or more subjects that were not described in the protocol or consent form;
- Any unapproved change or modification to an IRB-approved protocol (deviation), intentional or unintentional, that places one or more subjects at risk, affects the integrity of study data, or that has the potential to recur;
- Changes to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a subject;

- Complaints that indicate unexpected risks, or complaints that cannot be resolved by the PI;
- Malfunctioning of research equipment that results or could result in risk to subjects or others;
- A laboratory reagent used in the research found to be a potentially dangerous carcinogen, posing a risk to the laboratory workers;
- Interim findings (data analysis and/or safety reports) or research monitor reports that indicate that the frequency or magnitude of harms or the potential benefits of the research may be different than initially presented to the IRB;
- Publications in the literature that indicate an unexpected change to the risks or potential benefits of the research;
- Changes in FDA labeling, or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Breach of confidentiality or potential breach of research data (e.g., laptop containing identifiable private information is stolen or lost even if data files remain intact);
- Violations of applicable information security requirements;
- Loss of research data (e.g., paper records lost or destroyed, electronic records lost if hard drive crashes and data not backed up);
- Specimen storage is compromised (e.g., the freezer containing tissue samples collected for the study fails before specimens have been analyzed);
- Incorrect labeling, dosing, or dispensing of study medication or test article, even if there is no indication of harm (e.g., randomization error);
- Incarceration of a study participant when the investigator would like to keep the individual in the study;
- Disclosed pregnancy of participant;
- Unexpected disclosure of an event (e.g., child abuse) that requires reporting under state law;
- Any unanticipated event that influences the risk-benefit of the research.

**Adverse Events**

An adverse event (AE) is a recognized harmful or unfavorable outcome that has actually occurred to a research subject or to another individual being treated in a similar fashion in a relevant non-research setting. That is, an adverse event is an actual event, not a potential risk.

**Adverse Events for Research Studies that Involve Drugs or Devices that Require Prompt Reporting to the IRB**

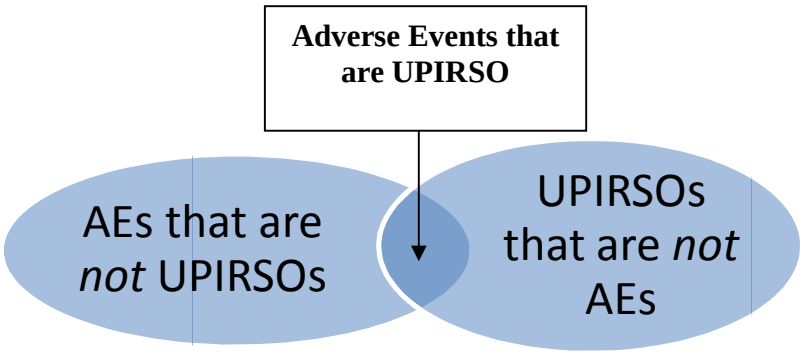
Adverse events that increase in frequency or are unexpected and related require reporting to the DDEAMC IRB. The investigator's input will be required on the issue regarding if the event was related to the research but the DDEAMC IRB will make the final decision.

**Difference between an "Unanticipated Problem" and an "Adverse Event"**

In contrast, an unanticipated problem may be either an actual harmful or unfavorable occurrence, or any development that potentially increased the likelihood of harm occurring in the future, or that reduced the likelihood of benefit of the research.

Whenever it comes to an investigator's attention that something has happened regarding the research that indicates the possibility that previously unsuspected harm may occur (or may occur at a higher than expected rate), that is an unanticipated problem and should be reported to the DDEAMC IRB according to the relevant guidelines.

Generally, when substantive changes in the research protocol or informed consent document, or other corrective actions are warranted in order to minimize the risk of harm to subjects, the problem is an unanticipated problem involving risks to subjects or others that requires prompt reporting to the DDEAMC IRB.




## 12.6 Serious Adverse Events (SAE) and Deaths

The PI shall report all serious adverse events (SAE) to the DDEAMC IRB via IRBNet and in compliance with Chapter 6 Policy #9 for the Deadlines for Submission by the PI to the IRB:

- Death due to *any cause*
- A permanent or substantial disability
- Hospitalization (inpatient admission or overnight stay) or prolongation of hospitalization
- An immediately life-threatening event
- Report of overdose (intentional or not)
- Report of congenital anomaly

## 12.7 Protocol Deviations from the IRB Approved Protocol

A deviation as noted in Definitions section above is considered to be any change or departure from the research activities outlined in the approved protocol, that is *under a researcher's control* and that has not been reviewed by the DDEAMC IRB and approved by the Institutional Official/Commander prior to its initiation or implementation. A protocol deviation may include accidental or intentional changes, including changes made to eliminate an immediate hazard to

subjects or others.

Note that unapproved departures from the study design or procedures that *are not under the control of the research team* are considered unanticipated problems.

Protocol deviations range in seriousness according to how the changes may impact participant safety, the degree of noncompliance with federal and state regulations and organizational policies, and the degree of foreknowledge of the event. Deviations may be minor or major as defined below.

**Minor Deviation -** Minor deviations, such as the performance of study-related tasks by qualified personnel not officially listed on the protocol, are to be reported to the DDEAMC IRB at the time of continuing review. Investigators should never plan a protocol deviation, unless to protect the rights, safety, or welfare of a subject. Committing a planned deviation may result in non-compliance sanctions.

A minor protocol deviation is one that does not:

- Substantially impact the rights, safety, or well-being of research subjects;
- Affect the value of the data collected
- Result from willful or knowing misconduct on the part of the investigators or study staff;
- Violate any ethical principles.

A change to research without prior IRB approval constitutes a "deviation." If an investigator makes an unapproved protocol change to eliminate an apparent hazard to subjects, the Principal Investigator (PI) must immediately report the change by phone or email to the Human Protections Administrator (HPA), IRB Chair and Chief, DCI. The PI then completes a Deviation Report, which must be submitted to the IRB within one (1) week of the deviation.

**Major Deviation –** A major deviation is one that adversely affects or may affect the rights, safety, or well-being of subjects; the integrity of the study data; or affects a subject's willingness to continue study participation. These may also be referred to as protocol violations. The DDEAMC IRB criteria for defining major deviations include any of the following:

- The deviation has harmed or posed a significant risk of substantive harm to research subjects;
- The deviation compromised the completeness, accuracy, and reliability of the study data;
- There is evidence of willful or knowing misconduct on the part of an investigator or study staff;
- The deviation involves serious or continuing non-compliance with federal, state, or local research regulations or flouting of ethical principles.

## 12.8 Research Monitor Responsibilities

Research monitor responsibilities are tailored to the study procedures and risks which are outlined in the IRB appointment memorandum by name and specific responsibilities. These responsibilities may include the review of events at any time during the research and if the

research monitor feels the nature, severity, or frequency of the adverse event is greater than described in the IRB-approved protocol and consent form, they are required to report this observation to the PI, HPA, and IRB Chair.

Exceptions are adverse events that are expected to occur frequently (e.g., headache at altitude) and that do not require medical care or cause a subject to stop the intervention or testing. The PI will forward notification of the medical event to the research monitor if one has been appointed for the study. If the incident was an unexpected adverse event, the research monitor will provide a written report within one (1) week of receipt of the initial report. If the event is a reportable event, the completed report will be submitted to the DDEAMC IRB. Submission of the written report to the IRB does not wait for the research monitor assessment.

**PI Responsibilities after Notification by the Research Monitor**

The PI will then submit a complete unanticipated problem report to the IRB one (1) week of learning of the unanticipated problem involving risk to subjects.

## 12.9 External Adverse Events/ IND Safety Reports

Investigators who conduct multi-site protocols usually receive a large number of reportable adverse events from sites that are not under the supervision of the DDEAMC PI. These reports rarely provide enough information to the DDEAMC IRB to ensure that they conduct a sound ethical and scientific review of the events in regards to the protocol and the subject pool. These reports may be called IND safety reports. It is unusual that these reports truly meet the definition of an unanticipated problem to subjects or others so it reasonable to presume that reporting of these will be rare instances.

Individual Unanticipated/Unexpected Problems and Adverse Events, involving risk to subjects or others, occurring at "external" sites will not be individually reported to the DDEAMC IRB. However, a "Summary Report" from the studies safety monitoring boards/committees last review addressing these issues, with a written statement from the local PI indicating a review of the report was completed and comments added on how/if the local study will be impacted/changed (or no change), will be reported at the time of continuing review.

An exception to reporting only at continuing review would be to submit the same safety board report to the IRB as soon as it is acquired if the report findings have a direct impact on the local study such as a required change to the protocol or consent form or a need to stop the study.

In no instances will "individual" "external" adverse event reports (serious or otherwise) be submitted to the DDEAMC IRB. Only summaries of these reports will be accepted in accordance with the guidelines previously provided.

## 12.10 Investigator Reporting to the IRB

The PI must report via IRBNet within one (1) week *any* situation or event that:

- Potentially alters the risk-benefit assessment of the research,
- May jeopardize the integrity of study results,

- May jeopardize the potential benefits to subjects or
- Prompts the Research Monitor to provide notification.

The investigator should include the following in the report to the DDEAMC IRB via IRBNet and should include:

- PI name and IRB identifier
- Detailed description of the problem/event/incident
- Explanation of the basis for determining that the problem/event is a UPIRSO
    - Unexpected
    - Study related
    - Increased risk to subjects or others
- Description of actions already taken, other corrective actions proposed, and proposed changes to the protocol in response to the unanticipated problem

## 12.11 DCI Research Regulatory Compliance Office (RRCO) Staff Responsibilities upon Receipt of a Reportable Event

The DDEAMC DCI RRCO staff and IRB [32 CFR 219.105(b)] should process the UPIRSO with the following procedure:

1. Protocol coordinator conducts an administrative review and shares the information with the following:
    a. HPA
    b. IRB Chair and/or Vice Chair
2. The HPA and/or IRB Chair will review the information provided for the reported event and determine if:
    a. Additional information is needed from the research team
    b. Additional information is needed from the affected individual(s) independently of the research team
3. Once the information is complete the HPA and/or IRB Chair will review and assess the facts of all reported events, to include reviewing the related IRB records and the current approved protocol and consent form. The reviewer may request any clarifications, corrections, or revisions to the report if needed to evaluate the event or problem from the PI or other research team member. The HPA and/or IRB Chair will also determine the following:

| | Yes | No |
|---|---|---|
| Was the event unexpected? | | |
| Was the event related, or possibly related, to the research? | | |
| Did the event place subjects or others at a greater risk of harm than was previously known or recognized as described in the protocol? | | |

If all three answers are yes, then the event was a UPIRSO and further investigation should occur as outlined below. If any of the answers above are no, then the event was not a UPIRSO and further investigation and reporting as a UPIRSO is not required.

4. If the event was reported as serious adverse event, the HPA and/or IRB Chair will determine if the event was a SAE. The IRB Chair or designee will review the reported event and determine the type of event. The appropriate management of an event with an adequate corrective action plan (CAP) and resolution will be accepted by the IRB Chair or designee and documented in IRBNet. The PI will be instructed to include the event in the summary at the time of continuing review. The report will be filed in the IRB records. The event will then be reported to the convened IRB at its next scheduled meeting.
5. If the event was a UPIRSO and there is an immediate risk to human subjects or others, the DDEAMC IRB Chair or Institutional Official/Commander may require the PI to suspend the study. Any such action shall be communicated via IRBNet and will include a statement of the reasons for the IRB action. This documentation will be stored as part of the official protocol file. This action will be reported to the IRB at the next convened meeting. During their review, the HPA and/or IRB Chair will:

    a. Identify the cause of the problem (root cause analysis)
    b. Identify risks to subjects (actual, potential)
    c. Identify risks to others (actual, potential)
    d. Identify corrective actions to protect subjects/others
    e. Identify corrective actions to prevent recurrence (protocol specific, system wide)
    f. Identify who needs to be informed (including when and how)
    g. Assign the UPIRSO for additional review as necessary based on the severity of the event by either:
        1. The IRB Chair and/or Vice Chair
        2. A subcommittee as appointed by the HPA and IRB Chair
        3. The convened IRB

## 12.12 Convened Meeting Review

### RRCO Staff Responsibilities

The RRCO ensures DDEAMC IRB members are notified and the documents listed below are made available for review via IRBNet at least three (3) business days prior to the meeting when problem reports are reviewed by the convened IRB.

The RRCO staff records the discussion, rationale for any action, and vote in the minutes. Any required action shall be communicated via IRBNet to the PI. The notification will include a statement of the reasons for the IRB action.

### IRB Member Responsibilities

All IRB members will have access via IRBNet to the following documents that should be reviewed prior to the meeting as well as to engage in any discussions that occur at the convened meeting:

- Event Report Form;
- Currently approved protocol;
- Currently approved informed consent form (ICF);
- Previous reports of unanticipated events and problems involving risks to subjects or others (UPIRSOs), if they exist.

**IRB Chair Responsibilities at the Convened IRB**

The IRB Chair or designee acts as the primary reviewer and presents their initial findings to the convened IRB.

**Convened IRB Review of the UPIRSO**

The DDEAMC IRB may interview the PI or the researcher who reported the problem.

1. The reviewers must determine if the protocol still meets all approval criteria as outlined in 32 CFR 219.111 (including risk, benefit, informed consent, etc.).
2. If the protocol still meets all approval criteria, then the determination will be made if the event is a UPIRSO. If not, reporting obligations are not triggered IAW 32 CFR 219.103(a) and (b) (5).
3. The DDEAMC IRB has authority to require additional information and/or changes as condition of continuing approval IAW 32 CFR 219.109(a).
4. Any proposed changes must be approved by the IRB before implementation except when necessary to eliminate apparent immediate hazards to subjects.
5. The convened IRB evaluates the event by considering whether the problem is an UPIRSO and then votes on whether the report is an UPIRSO.
    - If the report was not an UPIRSO, the PI will be instructed to include the event in a summary of adverse events at the time of continuing review and no additional actions will be required.
6. If the report was determined by the DDEAMC IRB to be an UPIRSO, then the DDEAMC IRB must also determine:
    - If the event involved a protocol deviation consider whether the incident relates to serious or continuing non-compliance
    - Whether the risk/benefit ratio of the research has become less favorable from that posed in the currently approved version of the protocol, and
    - Whether any actions other than those posed by the PI are necessary to ensure the ongoing safety of research subjects. Some examples of appropriate actions are:
        - Modification of the research protocol;
        - Modification of the information disclosed during the consent process;
        - Additional information provided to past subjects;

- Notification of current subjects (required when such information may relate to subjects; willingness to continue to take part in the research);
- Requirement for current subjects to re-consent;
- Alteration of the frequency of continuing review;
- Observation of the research or the consent process;
- Requirements of additional training of the PI and/or other members of the research team;
- Suspension of the research until corrective action is taken;
- Termination of the research;
- Requirements of the PI to show competency in related aspects of the ethical and regulatory requirements of human subjects research before approving other studies submitted by the investigator;
- Requests of additional information from the PI, research team members, or study subjects;
- Disciplinary measures taken against the PI or other research team members;
- No further action (if appropriate).

## 12.13 Reporting to the Appropriate Institutional Officials and Department and Agency Heads

It is the responsibility of the DDEAMC IRB and RRCO to assure that reporting occurs according to the federal regulations IAW 32 CFR 219.103(a) and (b)(5), and DDEAMC policy. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm. Prompt is determined to be within one (1) week of becoming aware of the event.

The DDEAMC IRB and RRCO will follow the procedures below for assuring prompt reporting to the IRB, appropriate institutional officials, CIRO, and the AHRPO:

a. Any unanticipated problems involving risk to subjects or others;
b. Any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB;
c. Any for-cause suspension or termination of IRB approval.

**Institutional Official/Commander Responsibilities:**

The Institutional Official/Commander will assure notification of CIRO and AHRPO by email within one (1) week of becoming aware of a reportable event.

**RRCO Responsibilities:**

1. This reporting will take place within thirty (30) days of the completion of an investigation and determination.
2. The notification of an investigation into reports or allegations of serious or continuing non-compliance will be sent by email within one (1) week of the IRB or RRCO learning of the incident (32 CFR 219 (b)(5)) to CIRO and AHRPO.

3. Each letter with the supporting report will be initially drafted by the HPA and include the following information for DDEAMC and its MTF:
    a. Assigned IRB number
    b. Title of the research project
    c. Name of the principal investigator
    d. The nature of the event;
    e. The findings of the organization and IRB;
    f. Actions taken by the organization or IRB;
    g. Reasons for the organization's or IRB's actions;
    h. Plans for continued investigation or action.
4. The letter with the supporting report is sent to the following for review and approval.
    a. The IRB Chair
    b. Chief, DCI
    c. The Institutional Official/Commander
5. Edits are incorporated by the HPA and the letter is signed by the Institutional Official (IO)/Commander.
6. The HPA sends a copy of the signed letter to the following:
    a. IRB Members via IRBNet
    b. The appropriate Careline/Department Chiefs
    c. CIRO
    d. AHRPO
    e. Study sponsor, if the research was sponsored (this includes Henry M. Jackson Foundation and industry sponsors)
    f. Principal Investigator (PI)
    g. DHHS OHRP in compliance with the federal wide assurance (FWA) if the research is conducted or funded by the DHHS

## 12.14 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.

9. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
10. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
11. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
12. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
13. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
14. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
15. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
16. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 13: Investigator Responsibilities and Duties

## 13.1 Purpose

The purpose of this policy is to direct investigators, institutional review board (IRB) members, and Institutional Officials (IO) about the required investigator responsibilities and duties as a component of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 13.2 Background

Principal Investigators (PIs) must follow requirements for conducting research and comply with all applicable federal, Department of Defense (DoD), Department of the Army (DA), and the Dwight D. Eisenhower Army Medical Center (DDEAMC) regulations and policies and procedures for protecting research subjects. General responsibilities of the Investigator are included in Chapter 1, Framework.

The protection of research subjects is the shared responsibility of principal investigators (PIs), Careline/Department Chief, members of the research team, and the DDEAMC Institutional Review Board (IRB). However, the ultimate responsibility for the safety and welfare of research subjects lies with the PI and as such the PI must:

- Design studies that are scientifically sound (using policies and procedures outlined in the Human Research Protection Program [HRPP]) and will yield valid results;
- Be qualified to conduct the research and be trained in human research protection ethical principles, regulations and policies, and procedures, and ensure all research personnel are trained and supervised;
- Ensure that the research has been approved by the proper review committees before starting, modifying, or extending the research;
- Conduct the study according to the protocol approved by the DDEAMC IRB and apprise the IRB of noncompliance with the approved research protocol;
- Ensure that subjects are fully informed of the nature of the research to include potential risks associated with study participation;
- Disclose potential conflicts of interest (COI) as outlined in Chapter 3 Conflict of Interest;
- Promptly report new information, modification(s), or adverse event(s) as defined in Chapter 6;
- Ensure that the rights of subjects are protected, including privacy and confidentiality of collected data;

- Apply relevant professional standards;

- Prepare and maintain records and reports associated with the research.

## 13.3 Qualifications of PI and Research Staff

Personnel covered by DDEAMC Assurances document the completion of the required education on human research subjects by the successful completion of the Collaborative IRB Training Initiative (CITI). The DCI Research Regulatory Compliance Office (RRCO) staff along with the DDEAMC IRB members ensures that PIs and research staff are qualified by training, education, and experience for their research roles.

### Verification of Training and Experience

The PI and research staff involved in the design or conduct of a study is responsible for providing evidence of training, education, and other qualifications by submitting relevant documentation to the DDEAMC IRB. Proof of training in the protection of human research subjects (Collaborative Institutional Review Board Training Initiative, CITI) is a condition for approval of research credentials and must be submitted to the DDEAMC IRB at the time of initial protocol review. The credentials of the PI and research staff are evaluated at the time of continuing review and when study personnel are added.

### Relevant Professional Standards

PIs must exercise professional judgment at all times and adhere to the principles that the rights of subjects are more important than the pursuit of knowledge

PIs must always ensure that:

- Research subjects are informed of their role throughout the research process;
- They mitigate any perception of coercion or undue influence.

## 13.4 PI Responsibilities

### 1. PI Reporting to the DDEAMC IRB — Reportable Events

The PI will assess and report unanticipated problems occurring during a research study in accordance with applicable federal, DoD, DA, and DDEAMC regulations and policies and procedures. Chapter 12 Reportable Events including Unanticipated Problems and Serious Adverse Events provides definitions and report guidance of unanticipated events.

The PI must first assess and then, if appropriate, promptly report to the IRB any reportable events including unanticipated problems involving risks to study subjects or others (UPs), and other reportable information as required in Chapter 12 Reportable Events including Unanticipated Problems and Serious Adverse Events.

Events requiring reporting are discussed in Chapter 12 Reportable Events including Unanticipated Problems and Serious Adverse Events. Reporting timeframes are discussed in Chapter 6 Policy #10 Deadlines for Submission by the PI to the IRB.

Initial reports must be submitted by these deadlines, even if there is insufficient information for a complete report. Follow-up reports will be submitted when complete information is available.

### 2. Protocol Amendments

When an event or new information prompts a revision to previously approved research (e.g., new side-effect in the consent form), the protocol is modified and approved by the IRB prior to implementation. The only exception to pre-approval is for a modification necessary to eliminate apparent immediate hazard to the research subjects; in such a case, the PI must notify the DDEAMC IRB of a protocol deviation. See Chapter 6 Policy #7 Amendments for guidance on the submission requirements and Chapter 6 Policy # 10 Deadlines for Submission by the PI to the IRB for timeframe/deadline requirements.

### 3. Submitting Regular "Routine" Reports

The PI must submit Continuing Review reports as directed by the DDEAMC IRB in order to conduct the research study. See Chapter 6 Policy #8 Continuing Review for guidance on the submission requirements and Chapter 6 Policy #9 Deadlines for Submission by the PI to the IRB for timeframe/deadline requirements.

### 4. Research Oversight

PIs must maintain appropriate oversight of their research protocols and research staff during recruitment, selection of study subjects, and study conduct. PIs retain ultimate accountability for the conduct of those to whom they delegate research responsibilities.

### 5. Initial/New Protocol Submission

Research protocols that involve the use of human subjects or data or specimens from humans must be submitted to the DDEAMC IRB for a scientific and human use review for approval prior to the initiation of any study activity. The protocol shall make provision for the adequate protection of the rights and welfare of prospective research subjects and ensure that pertinent laws and regulations are observed.

The research protocol outlines the specific procedures that will be followed during the course of the study. The protocol must contain sufficient information for the reviewers to be able to adequately assess the scientific validity of the research plan and to make the appropriate determinations needed to approve research.

When preparing a protocol, each instruction or question should be addressed carefully and completely. In addition, correct spelling and grammar are essential to ensuring the clarity of the documents, especially for consent documents. Investigators must use the DDEAMC IRB Protocol Package Checklist to review their protocol package prior to submission to the RRCO via the IRBNet. Failure to do so will result in delays in the review of the protocol.

Documents and necessary forms required for review of new or continuing studies are provided in the DDEAMC's IRBNet site. It is the PI's responsibility to be aware of changes in submission requirements and use the most current forms and templates. The DCI Research Regulatory Compliance Office (RRCO) staff will update the IRBNet site as necessary. The PI is responsible for providing a research protocol that includes the below listed documentation.

| Documents Required Prior to Placement on IRB Agenda | Forms |
|---|---|
| 1. Complete and signed Application for Clinical Investigation Project | IRBNet |
| 2. Complete research protocol | PI provides |
| 3. For grant funded studies (e.g., CDMRP, NIH, etc.), complete grant application | PI provides |
| 4. All scales, data collection instruments and forms (e.g., survey instruments, questionnaires, interview scripts, etc.) | PI provides |
| 5. Informed Consent form(s) | DA Form 5303 MAR 2009 |
| 6. HIPAA Authorization(s) | Template FEB 2010 |
| 7. All advertisements, announcements, letters, or other recruiting materials | PI provides |
| 8. Letters of cooperation from field study site(s) not represented by a study investigator | PI provides |
| 9. Collaborating IRB approvals | PI provides |
| 10. CV of PI, dated within 1 year of protocol submission | PI provides |
| 11. Current CVs for Associate Investigators, Study Coordinator, and proposed Research monitor | PI provides |
| 12. Waiver request for consent and/or HIPAA, if applicable | PI provides |
| 13. Impact statements from all applicable services | PI provides |
| 14. MOU, MOA, CRADA, if applicable | PI provides |

Applications for review are to be submitted to the DDEAMC IRB via IRBNet. Most protocols require more than one revision because the DDEAMC IRB may request additional information or changes in the protocol, data collection instruments, or consent form. Investigators must leave sufficient time for review before the anticipated start date of the research. Research activity, to include recruitment of subjects, cannot begin until the Commander has approved implementation of the study.

## 6. Study Conduct and Amendment

If granted approval to conduct a research study, PIs must conduct the study according to the approved protocol. Any new information, modification, or unanticipated problem involving risks to the research subjects or others must be promptly reported to the IRB. Research subjects must be informed of any change that may affect their willingness to participate.

## 7. Informed Consent

Investigators are responsible for assuring the quality of the informed consent process and for making sure that proper consent is obtained and documented before subject participation, unless waivers are granted by the IRB. See Chapter 10 Informed Consent for guidance.

## 8. Privacy Rule (HIPAA)

When conducting research that involves the use and disclosure of protected health information (PHI), the investigator must abide by the applicable HIPAA policy of DDEAMC. See Chapter 10 Informed Consent for guidance.

## 9. Privacy of Subjects and Confidentiality of Records and Personal Data

Investigators must safeguard the privacy of research subjects and protect the confidentiality of personal information collected over the course of their participation by:

- Establishing, maintaining, and documenting mechanisms used to safeguard personal information throughout the research process,
- Maintaining confidentiality of research data when designing, implementing, conducting, and reporting research,
- Providing full information about the privacy and confidentiality of data to prospective subjects through the informed consent process,
- Avoiding unintentional breaches by taking precautions in communication, administration and storage of information.

## 10. Delegation of Research Responsibilities

The PIs may delegate research responsibility via IRBNet. In the event the PI must appoint an acting PI, the PI must notify the Careline/Department Chief by email or memorandum. A copy of the email or memorandum should be sent to RRCO for documentation in the official protocol file. An appointment in excess of three (3) months, or a replacement of the original PI, must be approved, through the Careline/Department Chief. However, PIs must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility.

The acting PI must be:

- Well trained and competent,
- A member of the research team, and
- Credentialed with like expertise as a human-use PI.

## 11. Continuing Review

It is the responsibility of the PI to ensure that continuing review is completed and renewal is approved by the DDEAMC IRB prior to the protocol expiration date (may be annually, semi annually, or more frequently). The continuing review report must be submitted in sufficient time to ensure the non-interruption of the study. See Chapter 6 Policy #7 Continuing Review for additional guidance.

## 12. Data Safety and Monitoring Plan (DSMP)

The PI (or designee as specified in the protocol) is responsible for monitoring research data to ensure the scientific integrity of the research and the safety of research subjects. Data monitoring is accomplished by assessing the quality and completeness of data collected, evaluating interim findings, and reviewing recent publications that are relevant to the current study. The Research monitor, if appointed, will continuously monitor the safety of subjects by evaluating whether the character, incidence, and severity of adverse events match those expected. See Chapter 12 for guidance on the submission requirements and Chapter 6 Policy #10 Deadlines for Submission by the PI to the IRB for timeframe/deadline requirements as these chapters provides definitions, responsibilities, and time frames for reporting adverse events and unanticipated problems.

## 13. Oversight of Research Staff during Recruitment

The PI is responsible for ensuring that informed consent is obtained from each research participant before that individual participates in the research study. The PI may delegate the task of obtaining informed consent to an associate investigator (AI) in writing via IRBNet. The AI must be knowledgeable about the research while the PI retains ultimate responsibility. See Chapter 10 Informed Consent for guidance.

## 14. Selection of Study Subjects

The PI must ensure that participant selection complies with the DDEAMC IRB approved inclusion and exclusion criteria. Adequate protections for subjects, as outlined in the IRB approved protocol, must be ensured during the conduct of research.

The PI must take special care to consider issues such as the selection of subjects at risk for being discriminated against or over-selected, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. See Chapter 9 Policy Research Subject Selection and Recruitment for guidance.

## 15. Study Conduct

The PI is responsible for:

- Conducting all aspects of the study and for activities of the research team.
- Conducting the study scientifically and ethically.
- Ensuring the use of appropriate methods and correct procedures, according to the approved protocol.
- Promptly reporting any new information, modification, or unanticipated problems to the DDEAMC IRB and research subjects informed of any change that may affect their willingness to participate.
- Assure that all personnel under his or her supervision are adequately trained, privileged (if applicable), and supervised.
- Delegate research duties to individuals that are qualified to perform the assigned tasks.

**16. Compliance with the IRB**

The PI must assure compliance with the DDEAMCIRB. Federal, DoD, and DA regulations require research involving human subjects to be reviewed and approved by an IRB, i.e., the DDEAMC IRB A detailed discussion of the roles and responsibilities of the DDEAMC IRB is available at Chapter 6, Policy #1 IRB.

Non-compliance with the approved protocol must be reported promptly to the DDEAMC IRB as required in Chapter 12 Reportable Events including Unanticipated Problems and Serious Adverse Events. Reporting timeframes are discussed in Chapter 6, Policy #10 Deadlines for Submission by the PI to the IRB. Chapter 6, Policy #7 Amendments for guidance on the submission requirements details the policy and procedures for making amendments to approved protocols.

**17. Adhere to Timelines**

All timelines are outlined in Chapter 6, Policy #10.

**18. Transfer of Protocols or Data**

Investigators that deploy or leave DDEAMC or its MTFs covered under the Assurances are required to transfer the research records to a new PI or their Service Chief within their departing MTF. Custody of all original data must be retained by the research division in which they were generated. An investigator who moves to another institution may submit to the Commander a written request to remove copies of the data from the organization. This request must contain an itemized description of the data and must specify where the data will be located in the future.

## 13.5 References:

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. December 28, 2001.
3. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2000.
4. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
5. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
6. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
7. Department of Defense Instruction 3216.02. *Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*. November 8, 2011.
8. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
9. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
10. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 14: Non-Compliance with Human Research Protection Program Requirements

## 14.1 Purpose

The purpose of this policy is to provide information about the identification, investigation, determination, and required reporting of non-compliance with the requirements of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 14.2 Background Information

Non-compliance occurs when unapproved changes are made to the protocol except when necessary to eliminate apparent immediate hazards to subjects [32 CFR 219.103 (b)(4)]; when IRB requirements or determinations are not met [32 CFR 219.103 (b)(5)]; and when the requirements of the Common Rule are not met (by anyone governed by this regulation, including the institution, the IRB, and investigators) [32 CFR 219.103 (b)(5)].

Federal regulations require that IRBs have procedures for prompt reporting to the IRB, appropriate institutional officials, and relevant federal departments or agencies any serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB. Ensuring that serious or continuing non-compliance with the Human Research Protection Program (HRPP) requirements is promptly reported and effectively addressed is essential to protecting the rights and welfare of research subjects and to the integrity of the HRPP.

In order to ensure appropriate oversight of research activities, the DDEAMC IRB will investigate all allegations of research regulatory non-compliance. The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with HRPP policies, or is not in compliance with federal regulations (32 CFR 219.113) or state law[1]. Serious or continuing non-compliance and suspensions or terminations of IRB approval must be promptly reported to the Clinical Investigations Regulatory Office (CIRO), USAMRMC Human Research Protections Office (HRPO) in accordance with 32 CFR 219.103 (b)(5).

## 14.3 Definitions

***Non-Compliance***: As used in this policy, non-compliance means failure of a person or organization to follow federal and state regulations, as well as institutional policies and guidelines, for human subject protection or with the requirements or determinations of the DDEAMC IRB.

***Continuing Non-Compliance***: Repeated instances of non-compliance. Continuing non-compliance indicates a lack of attention to or knowledge of the regulations or policies or a willful disregard of IRB requirements.

***Minor Non-Compliance*:** Occasional instance of non-compliance that is neither serious nor continuing. Examples include these:

- Failure to complete HRPP education requirements in a timely manner,
- Late report of an adverse event that did not impact the risk/benefit relationship of the study, or require modification of the informed consent,

[1] State laws apply when research is conducted off of a military installation.

- Single instance of failure to submit a continuing review report to the DDEAMC IRB in time to prevent the lapse of approval,
- Failure to provide IRB requested information,
- Failure to obtain date of participant signature on a consent form
- Use of an outdated informed consent form (ICF) that is identical to the currently IRB-approved consent form, or identical in all material respects (e.g., change in the name of an Associate Investigator),
- Minor over enrollment of IRB-approved accrual goal in a minimal-risk research study.

***Serious Non-Compliance:*** An action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risks to subjects, decreases potential benefits or compromises the integrity or validity of the research. Examples of serious non-compliance include, but are not limited to the following:

- Failure to obtain DDEAMC IRB approval of human subjects research,
- Failure to obtain IRB approval prior to implementation of a change in the research,
- Failure to obtain informed consent from a participant,
- Enrolling research subjects who do not fit the inclusion and exclusion criteria in the protocol,
- Failure to respond to a request to resolve an episode of non-compliance.

## 14.4 Non-Compliance

**Possible Sources for Allegations of Non-Compliance**

Allegations or reports of non-compliance may arise from the following:

- Study investigators or staff,
- DDEAMC IRB members or Research Regulatory Compliance Office (RRCO) staff (e.g., when discovery is made during a continuing review),
- Continuing monitoring programs such as the Department of Clinical Investigations (DCI) and HRPP publications clearance process,
- Research subjects or potential subjects,
- Others not involved in the research project, but having information about possible non-compliance.

**Immediate Reporting After Discovery of Possible Non-Compliance**

Anyone who has reason to believe that non-compliance has occurred should report this fact to the RRCO or DDEAMC IRB Chair as soon as possible after discovery. Reports can be submitted in person, via telephone, email or letter. The report, whether verbal or written, should include the following:

- Title or description of the research project in which the non-compliance occurred,
- Detailed information about the alleged or confirmed noncompliance, including relevant dates,
- Information about any injury, potential harm, or risk to a participant or others,
- How the person reporting obtained the information,
- How the reporter may be contacted for further information, if needed,
- Any other relevant information.

If subject safety is at risk, the DDEAMC IRB Chair, HPA or Department of Clinical Investigations (DCI) Chief should be immediately notified.

***The RRCO staff and the DDEAMC IRB will preserve the confidentiality of all parties involved and will utilize due process.***

**Formal Written Report of Non-Compliance**

Investigators and research staff must report all allegations or incidents of non-compliance within five (5) business days of learning of the occurrence to the RRCO or the DDEAMC IRB Chair. The initial report should be in writing (through Careline/Department Chief and HPA for Chair, IRB), and contain the following:

- Title and protocol number (if known) of the research project in which the non-compliance occurred,
- Name of the PI,
- Detailed information about the alleged or confirmed noncompliance, including relevant dates,
- An assessment of whether any subjects or others were placed at risk as a result of the compliance or suffered any physical, social, or psychological harm,
- Any corrective action, planned or already taken, to ensure that the noncompliance will not occur again,
- Any other relevant information.

## 14.5 Procedures for Handling Allegations and Reports of Non-Compliance

1. The RRCO staff will document receipt of the report of actual or suspected non-compliance. If the report was provided verbally and the reporter will not provide a written report, the receiver will document the allegations in writing.
2. If the report of non-compliance did not come from the PI, RRCO staff will obtain the investigator's response to the report.
3. The HPA will schedule a meeting with the DDEAMC IRB Chair to discuss and review the report and determine the appropriate course of action. If the potential non-compliance involves the IRB, the HPA will confer with the DCI Chief rather than the IRB Chair.
4. ***If there is any concern the potential non-compliance could be serious or continuing, the DDEAMC IRB Chair may immediately suspend the study.***
    - Any suspension of the research will be promptly reported to the Commander and the PI in writing.
    - The suspension and the reason for the decision will be scheduled for discussion at the next meeting of the DDEAMC IRB. The IRB will determine whether to lift or continue the suspension. The IRB will promptly notify the PI and the Commander of its decision. IRB discussion and resolution of the non-compliance issue relating to the suspension may be scheduled for a subsequent IRB meeting.

**Preliminary Review**

1. The DDEAMC IRB Chair and HPA, with assistance of any designated IRB members, will conduct a preliminary inquiry to determine the truth of the allegation and whether the incident represents serious or continuing non-compliance. The scope of the inquiry will initially be limited to the allegation, but could expand if indicated by the findings. They may interview (in person, by telephone, or email) the PI, members of the study team, and other relevant witnesses. The IRB may review the laboratory notebook, signed informed consent documents, research data, medical clearance records, and any other relevant information.
2. Potential findings and outcomes of preliminary inquiry:
    - If the DDEAMC IRB Chair and HPA determine that the allegation of non-compliance is not supported by facts, they will inform the PI in writing of this determination. No further action will be taken.
    - If the DDEAMC IRB Chair and HPA determine that there was non-compliance that was neither serious nor continuing and all parties mutually agree on a corrective action plan, the determination will be filed in the IRB records and no further action will be taken. The IRB will be informed of the determination of minor non-compliance at the next meeting. If more than minor modifications are needed, the convened IRB must review the amendment.
    - If the DDEAMC IRB Chair and HPA determine that the allegation or finding meets the definitions of serious or continuing non-compliance, the Chair shall report in writing this finding to the Commander, and the matter will be placed on the agenda of the next IRB meeting for review by the convened IRB.
    - In cases where the preliminary review suggests that an investigator has demonstrated an apparent pattern of disregard for research regulations, policies, or procedures, further DDEAMC IRB review may be recommended even when the specific finding of non-compliance is resolved informally.
3. The RRCO staff will provide the results of the preliminary review in writing to the investigator within 30 days of commencement of the review. In cases where the DDEAMC IRB finds that further review is necessary, the PI's Department Chief and the Commander will be copied on this communication.

**IRB Review of Serious or Continuing Non-Compliance**

1. Preliminary findings of serious or continuing noncompliance will be reviewed at a convened meeting of the DDEAMC IRB using the primary reviewer system. The IRB Chair will usually be the Primary Reviewer. The RRCO staff will forward to all members, prior to the meeting, the initial report, and results of the preliminary review, and the latest approved protocol and consent form, latest approval letter from the Commander, and other relevant protocol documents using IRBNet. The IRB may need to review statements from investigators or research staff, IRB correspondence, or HRPP policies and procedures.
2. The DDEAMC IRB review considerations will include the following:
    - Identifying the problem (Is it non-compliance? Is it a UPIRSO?)
    - Identifying the cause of the non-compliance
    - Identifying actual and potential risks presented by the non-compliance
    - Identifying corrective actions for the non-compliance

- Identifying corrective actions to prevent recurrence (protocol specific and/or system-wide)
- Identifying who need to be informed (including when and how).

3. If the DDEAMC IRB substantiates the finding of serious or continuing non-compliance, the Committee will identify the activities that resulted in the non-compliance and determine corrective actions. The IRB may impose any one or a combination of the actions listed below:
   - Modifying the research protocol, procedures, and/or information disclosed during the consent process,
   - Monitoring the research,
   - Monitoring the consent process,
   - Auditing the active protocol,
   - Requiring more frequent continuing review or interim reports,
   - Suspending or terminating the research (considering impact on current subjects),
   - Requiring additional human research protections training of investigative and research staff prior to re-approval of research,
   - Requiring transfer of research to a new PI,
   - Limiting the number or types of studies for which an individual may be PI,
   - Providing additional information to current or past subjects,
   - Consent or re-consent currently enrolled subjects.
4. The DDEAMC IRB may also recommend additional sanctions to the Commander:
   - Research privilege probation,
   - Suspension of research privileges,
   - Termination of research privileges,
   - Disallowing or qualifying the use for publication, or otherwise, of any data collected on the non-compliant research or by the non-compliant investigator,
   - Placement of letter of reprimand in investigator's personnel file,
   - Additional supervision or mentoring of the investigator.
5. The DDEAMC IRB shall, within a reasonable period of time, notify the investigator in writing of its decisions, with copies to the investigator's Department Chief and the Commander. However, the IRB shall not impose any final remedial action until the investigator has been given at least one opportunity to respond.
6. The investigator may, within a reasonable period of time, request that the DDEAMC IRB reconsider its final findings or actions. This request shall be in writing and shall adequately describe the basis for the investigator's request.
7. The DDEAMC IRB shall, at its sole discretion, determine whether to reconsider its final findings or actions in response to the investigator's request for reconsideration.
8. The DDEAMC IRB shall advise the investigator and the Commander, as appropriate, of its final determination and disposition regarding the investigator's request for reconsideration. Documentation pertaining to the non-compliance is maintained in the IRB files.
9. The RRCO will draft an incident report, for signature by the Commander, to the AHRPO, with copy furnished to USAMRMC HRPO.
10. The Commander or his designee will review the conclusions of the DDEAMC IRB, including any recommended actions and sanctions to address the non-compliance. The

decision to take disciplinary or other action against a non-compliant person is the sole discretion of the Commander or his designee.

## 14.6 Reporting to the Appropriate Officials and Department and Agency Heads

1. It is the responsibility of the DDEAMC IRB and RRCO to assure that reporting occurs according to the federal regulations, and DDEAMC HRPP policy. The IRB and RRCO will follow the below written procedures for assuring prompt reporting to the IRB, appropriate institutional officials, Clinical Investigations Regulatory Office (CIRO), and the Army Human Research Protections Office (AHRPO) Reference: 32 CFR 219.103 (b)(5):
    a. Any unanticipated problems involving risk to subjects or others;
    b. Any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB;
    c. Any for-cause suspension or termination of IRB approval.
2. The initiation of an investigation into reports or allegations of serious or continuing non-compliance will be sent by email within 24 hours of the DDEAMC IRB or RRCO learning of the incident.
3. This reporting will take place within 30 days of the completion of an investigation and determination.

**Procedures**

1. **IRB Chair Responsibilities.** The DDEAMC IRB Chair will report these items to the Chief, Department of Clinical Investigations, HPA, and Commander:
    a. Any event determined by the IRB to represent an unanticipated problem involving risks to subjects or others;
    b. Any non-compliance determined by the IRB to be serious or continuing non-compliance;
    c. Any action of the IRB to suspend or terminate a study's approval.
2. **Commander or Designee Responsibilities.** The Commander or Designee will notify HRPO and AHRPO by email within 24 hours of a report of serious or continuing non-compliance or serious adverse event.
3. **RRCO Responsibilities.**
    a. The HPA or designee will draft a letter describing the following:
        1. The nature of the event;
        2. The findings of the organization and DDEAMC IRB;
        3. Actions taken by the organization or DDEAMC IRB;
        4. Reasons for the organization's or IRB's actions;
        5. Plans for continued investigation or action.
    b. The letter is sent to the following for review and approval.
        1. DDEAMC IRB Chair;
        2. Chief, DCI and the
        3. Commander.
    c. Any edits are then incorporated into the letter.
    d. The letter is signed by the Commander.
    e. The HPA sends a scanned copy of the signed letter via email to the following:
        1. The DDEAMC IRB Members (as an item in the agenda packet);
        2. The appropriate Careline/Department Chief;

3. The USAMRMC, Office of Research Protections, Human Research Protection Office (hsrrb@amedd.army.mil);
4. The U.S. Army Human Research Protections Office;
5. Study sponsor, if the research was sponsored (this includes Henry M. Jackson Foundation, NSF, and industry sponsors);
6. The Principal Investigator (PI);
7. The DHHS OHRP, if the research is conducted or funded by the DHHS.

## 14.7 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. December 28, 2001.
3. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2000.
4. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
5. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
6. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
7. Department of Defense Instruction 3216.02. Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research. November 8, 2011.
8. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
9. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
10. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 15: Human Research Subject Education and Outreach

## 15.1 Purpose

The purpose of this policy is to describe the human subject education and outreach program of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 15.2 Background

Over the past ten (10) years, there has been a concentrated effort to increase the public's knowledge of available research education and the requirement for most research organizations to develop education and training regarding human subject research for all members of the HRPP. For research team members, the objective should be to actively recruit and appropriately retain subjects of the most diverse study population consistent with the purposes of the research project. Indeed, the purpose should be to establish a relationship between the investigator(s) and staff(s) and populations and community(ies) of interest such that mutual benefit is derived for subjects in the study. Investigator(s) and staff(s) should take precautionary measures to ensure that ethical concerns are clearly noted, such that there is minimal possibility of coercion or undue influence in the incentives or rewards offered in recruiting into or retaining subjects in studies. It is also the responsibility of the IRBs to address these ethical concerns.

## 15.3 Addressing Concerns of Research Subjects

It is the policy of DDEAMC to maintain or utilize confidential and reliable channels for current, prospective, and former research subjects to ask questions, voice concerns, or register complaints about research activities.

The DDEAMC Institutional Review Board (IRB) requires that each informed consent document includes specific language on whom to contact for answers to pertinent questions about the research, who to contact for answers to pertinent questions about research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

The most appropriate contact for questions about the research is usually the Principal Investigator (PI); however, in some studies the subjects may additionally be directed to the study coordinator or a more available associate investigator. Subjects will be provided the phone number in the informed consent form for the Human Protections Administrator (HPA) as an informed individual who is independent of the research team, if they have any concerns, complaints or general questions about the research or their rights as a research subject. Subjects should be provided the name and telephone number of the Research Monitor if appointed, or contact information for the primary health care provider providing medical coverage of the study in the informed consent form. They will also be given information on how to, in case of injury, contact the Center Judge Advocate at DDEAMC. For studies enrolling subjects from outside the immediate geographical area, the consent form must provide a toll-free number.

The Consent Form template, available via IRBNet Forms, instructs investigators to include appropriate contact information in their consent forms. The IRB Primary Reviewer uses the current version of the *DDEAMC IRB Primary Reviewer Consent Checklist* to ensure the

appropriate contact information sections are contained in the consent form. Prior to approval, the DDEAMC IRB will confirm that appropriate mechanisms are in place to allow subjects to ask questions and voice concerns or complaints to the investigators.

The Human Protections Administrator (HPA) handles all calls in a confidential manner. The HPA may note the caller's name and contact information. If the caller does not wish to provide that information, the caller will be treated in the same respectful and serious manner as with an identified caller. The HPA will take notes on the call and will follow-up with the Investigator, IRB Chair and others as necessary.

Depending on the nature of the call, the HPA may:

- Answer the question,
- Advise the subject to call the PI or research personnel directly, or
- May act as the liaison between parties.

If a serious allegation is made against the PI or a member of the research team, the HPA will initiate an investigation as outlined in HRPP Chapter on Non-Compliance.

## 15.4 Addressing Concerns of Staff

In order to have a strong HRPP, all research team members should feel free to bring any comments, concerns or complaints to the attention of the PI without any fear of professional harm or retribution.

The DDEAMC PIs are responsible for sharing and encouraging dialogue with all research team members including but not limited to associate investigators, clinical research coordinators as well as those individuals who perform services for the research but are not named as key personnel. This dialogue should be initiated prior to study start time and carried respectfully throughout the research as well as after the closure of the research study to ensure that opportunities to improve the research, clinical care, administrative actions or overall quality have been met. If there are significant issues such as safety issues, the PIs are required to share any documented concerns with the DCI, Chief; or the DDEAMC IRB Chair.

**Investigator Responsibilities**

To ensure the success of the research study and to facilitate an open channel of communication, the investigators should:

- Meet with the research team members on a regular basis to reviewing research study progress, and to discuss concerns about the research study as a whole or in regards to a single subject.
- Personally tell each research team member that it is their individual responsibility to raise any concern related to the conduct of the research without prejudice.
- Address each concern raised as a serious issue and review each concern with feedback to the individual who raised the concern.
- Not belittle or disrespect any research team member who conveys a concern.
- Promptly report to the DDEAMC IRB concerns raised that result in a reportable event as outlined in the DDEAMC HRPP documentation.

## 15.5 Disclosure of Research Results and Incidental Findings

### Incidental Medical Findings (Military)

In the event that a previously undisclosed or unknown medical problem is discovered either during the medical clearances process, or at any time while Soldiers are participating as DDEAMC research subjects, these will be treated in accordance with the American Medical Association's standards of Good Clinical Practice. Such findings automatically and immediately become sensitive and privileged medical information and all parties shall strictly protect the confidentiality of the information.

Any medical information that is discovered shall first be evaluated to determine whether immediate treatment or emergent evaluation is required; if so, then this subject's research activities shall cease, the subject will be triaged and referred to the appropriate level of medical care at once. Non-emergent, newly discovered medical information shall be reviewed to determine its potential impact upon the subject's ability to complete the research mission. Regardless of the type of medical information discovered, if the subject was previously unaware of it then, in general, it shall be discussed with her or him immediately, in private, by one of the licensed Health Care Providers (HCP). However, in some instances it may be more appropriate if the subject's Primary Care Provider, discloses and discusses the findings (if appropriate). Although each case will be different based upon the type of medical findings, at no time shall the subject be terminated from the study without a full disclosure of the findings, complete with an opportunity to discuss it at length with a licensed HCP and a plan for medical follow-up, as appropriate.

In the event that the subject has chosen to disclose this information to the research staff, then the PI shall ensure that everyone on his or her research team privy to the information shall also observe all HIPAA regulations and policies governing sensitive and confidential patient information.

### Incidental Medical Findings (Civilian)

In the event that previously undisclosed or unknown medical information is uncovered about a civilian research subject, either during the medical clearances process or during research activities themselves, this information shall immediately be discussed with them by a licensed health care provider on the research team or the Research Monitor (if one is assigned to the study). The information shall be treated as sensitive and privileged medical information and all parties shall strictly protect the confidentiality of the information.

In the event that the civilian subject has chosen to disclose this information to the research staff, then the PI shall ensure that everyone on his or her research team privy to the information shall also strictly protect the confidentiality of the information.

Information discovered about civilian subjects shall be given to them immediately, and passed on to the subject's Primary Care Provider if they so request. This information will be evaluated by the Research Monitor to determine whether it will affect the individual's research participation. The Research Monitor shall utilize the standards of Good Clinical Practice when making medical decisions about research subjects. With civilians, this may

involve communications with their health care providers, which the Research Monitor will initiate at the individual's request.

## 15.6 Subject and Community Outreach

With the addition of a full-time HPA to the RRCO staff, DDEAMC will focus on developing a strong Human Research Subject/Subject Education and Outreach Program. This program will include:

- Evaluation of research subjects' understanding of research studies through active monitoring of the informed consent process.
- Active engagement in the local military and civilian community to assist in identifying cultural and community factors that may affect the DDEAMC IRB's ethical review of protocols.
- A focus on providing information to research subjects on their rights.

## 15.7 HRPP Education

The required HRPP education of the DDEAMC IRB members, DCI staff and members of the research team such as principal investigators, associate investigators, study coordinators, etc. is covered in the HRPP Chapter on Education.

## 15.8 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
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13. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
14. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
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## 15.8 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
9. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
10. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
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12. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
13. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
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15. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
16. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006

# Chapter 16: Dissemination of Research Findings

## 16.1 Purpose

The purpose of this policy is to provide direction about the appropriate process for the dissemination of research findings from Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 16.2 Background

DDEAMC ensures that the benefits of knowledge obtained through research are realized and that the interests of current and future research participants are protected. For the benefits of research to be realized, the results must be shared with the military or scientific community. Investigators have a responsibility to present or publish the results of their research.

## 16.3 Policy

DDEAMC expects its contributions to research to receive due credit in articles, presentations, interviews, and other forms in which the results of that research are publicized. This requirement also applies to situations in which DDEAMC Assurances cover military treatment facilities (MTF) provided no direct research funding, but the research involved the use of other organizational resources, e.g., facilities or investigator's salaries. It is the responsibility of the research investigators to comply with this policy.

DDEAMC will not enter into a cooperative research agreement or accept a grant to carry out research if the agreement or grant restrains the freedom of DDEAMC to disclose the research results. In a program of research conducted under a Cooperative Research and Development Agreement (CRADA) or Memorandum of Understanding (MOU), provision may be made for a short delay in the publication of research results, (the period of delay normally not to exceed 90 days), for patenting purposes or for collaborator review of and comment on manuscripts, providing that no basis exists at the beginning of the project to expect that the collaborator would attempt either to suppress publication or to impose substantive changes in the manuscripts.

The publication of research results by institutions conducting contracted research for DDEAMC shall be governed by terms of the contract. The contract terms shall allow for review by DDEAMC, and acknowledgement of Department of the Army support.

## 16.4 Requirements and Responsibilities

### Investigator

Before a scientific abstract or manuscript is submitted for publication or presentation, the author/presenter must obtain review and approval of the document/presentation.

The individual must also obtain official clearance for the publication/presentation. The publication or presentation must be reviewed to ensure defense security requirements including the provisions of AR 530-1, The Army Public Affairs Program, are satisfied. The information should be submitted via IRBNet.

**Chief, Department of Clinical Investigation (DCI)**

The Chief, DCI or designee will verify, through the Human Protections Administrator (HPA), if the abstract, manuscript or presentation is the result of a protocol approved by the DDEAMC Institutional Review Board (IRB) or was approved as an exempt study. The Chief, DCI serves as the approving official for research related abstracts and manuscripts intended for presentation or publication. This approval will be documented via IRBNet.

**Public Affairs Officer (PAO) and Security Officer (SO)**

The PAO and SO will ensure that the abstract, manuscript or presentation complies with the criteria published in AR 360-1.

## 16.5 Required Statements

All publications and presentations of DDEAMC human subjects' research results shall contain the following statements:

- Approved for public release; distribution is unlimited.

- The investigators have adhered to the policies for protection of human participants as prescribed in Army Regulation 70-25, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

- Disclaimer Statements: The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or reflecting the views of the Army or the Department of Defense.

The following statement must be included if specific brand names or commercial products were utilized during the study:

> ***Any citations of commercial organizations and trade names in this report do not constitute an official Department of the Army (DA) endorsement of approval of the products or services of these organizations.***

## 16.6 Publication Clearance

All written materials, including manuscripts, abstracts, and book chapters reflecting the DDEAMC or one of its covered MTFs under the Assurances, must be cleared through the Commander and DDEAMC Public Affairs Officer (PAO) and the Security Officer (SO). The following publications and abstracts require DDEAMC approval:

- Reports citing a MTF covered under DDEAMC Assurances in the title or byline;
- Reports of DDEAMC approved research projects;
- Reports of research performed by staff (military, civilian or contractor) assigned to MTF covered under DDEAMC Assurances.

Proper clearance must be obtained ***before*** the publication is submitted (journal, book, meeting, etc.)

## 16.7 References

The following references are provided for informational purposes:

1. AR 360-1 The Army Public Affairs Program 15 September 2000
2. AR 530-1 Operations Security 19 April 2007
3. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 17: Communication

## 17.1 Purpose

The purpose of this policy is to provide information about the communication plan that the Human Research Protection Program (HRPP) via the Department of Clinical Investigation (DCI) at the Dwight D. Eisenhower Army Medical Center (DDEAMC) utilizes to inform the research community about any changes, updates, educational topics, etc.

## 17.2 Background

It is valuable to all members of the research community to understand the process of communication between those members. This process includes the Defense Medical Research Network (DMRN) IRBNet and IKENet to disseminate new policies and procedures as well as changes and updates. All members of the research team have a responsibility to stay informed of any policies that may have an impact on their operations.

## 17.3 Policy

The DCI's is responsible for ensuring constructive communication among the Research Regulatory Compliance Office (RRCO), Careline/Department Chief, research investigators, DDEAMC Institutional Review Board (IRB) members, Institutional Official, and the Command Group as a means of maintaining a high level of awareness regarding the safeguarding the rights and welfare of research participants. The DCI Chief, Human Protections Administrator (HPA), and DDEAMC IRB Chair are responsible for overseeing all IRB communication with investigators.

All official communication between the DDEAMC IRB Chair, HPA, and investigators should be in writing to avoid miscommunication or misunderstanding and ensure an appropriate documentation trail. This documentation is accomplished via IRBNet for protocol related correspondence. The IRB Chair and HPA should refrain from verbal communications with investigators regarding official protocol/study issues. If informal conversations progress to implicit or explicit guidance or determinations, the IRB Chair will document and communicate the conversation in IRBNet.

Changes in policies and procedures related to the HRPP are communicated to all stakeholders via IKENet.

### Specific Interactions

The DCI Chief communicates regularly with the Commander (IO) and Command Staff about research and DDEAMC IRB business on a quarterly basis. The IRB Chair and HPA communicate regularly with the DCI Chief for advice, consultation, and notification of IRB determinations.

The DCI RRCO communicates directly with investigators through one-on-one consultations to offer advice and pre-screening services. However, all requests for revisions and clarifications on behalf of the IRB are done in writing.

See Chapter 6 Policy #2 for the documentation related to communicating the IRB decision to the PI.

The RRCO has access to be placed on the scheduled meetings such as:
- Commander Briefings
- Careline/Department Chiefs Meeting

Notifications to sponsors are made via the contract.

**Communication with Other Oversight Committees**
Other oversight committees such as the Radiation Safety Committee are part of the review process to ensure the highest level of human research protections. This interaction is usually completed via email.

## 17.4 Goals and Plans

The RRCO will be implementing a quality assurance program that will include conducting assistance reviews with PIs and at all of the military treatment facilities (MTFs) covered by DDEAMC's Assurances. One of the goals of this program will be to assure the protection of human subjects' rights and welfare through validating that protocol execution and documentation are being performed in compliance with the approved protocol.

The DCI RRCO website via DMRN or IKENet will be the primary location for documents to include:
- HRPP policies and procedures
- IRB standard operating procedures for research team members as well as the RRCO auditor
- IRBNet contains, or will contain, the following IRB templates such as:
  - Informed Consent Documents
  - Children's Assent Documents
  - Recruitment Materials

The Chief, DCI will pursue greater interaction with the Quality Management Department to ensure that projects are properly reviewed and included with performance improvement plans, if necessary.

It is anticipated that the DCI newsletter will be implemented again to provide information related to research at DDEAMC.

## 17.5 References:

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1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
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4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 18: Registries and Repositories

## 18.1 Purpose

The purpose of this policy is to provide direction for research that primarily involves the creation, collection or submission, storage and use over time of information and/or biological specimens in databases, registries and repositories at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 18.2 Background

Registries and repositories create rich environments for research. Both a registry and a repository may have been initially created with a clinical purpose such as diagnosis or disease tracking. The other alternative is that they may have been created with only research purposes in mind or the desire to have both clinical and research interaction. A data registry and a specimen repository can receive samples from multiple sources and they may send samples or data to multiple sources. The most outstanding attribute of a data registry or specimen repository is the ability to serve purposes over time as technology and knowledge change and grow. For ease of use the registry and repository may be considered as banks where deposits of data and samples are made. Each time that a withdrawal is to be made for a new research purpose, a new IRB protocol must be approved.

The federal human subject protection regulations at 32 CFR 319 and 45 CFR 46 as well as the federal privacy rule regulations at 45 CFR 160 and 164 provide regulation regarding the use of research databases, registries and repositories. The Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) provides additional guidance available at http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm). The guidance on the DHHS OHRP website further notes that a separate IRB review with approval for the following types of data registry and specimen repositories:

1) The collection of data or specimens
2) The operation of the repository as a storage and data management center
3) The use of data or specimens in research

The requirement for IRB approval of collection, repository and research protocols applies regardless of whether the repository was initially created for research or clinical purposes. Continuing review must occur for protocols that are registries or repositories.

## 18.3 Definitions

Biological Specimens - Any human material including but not limited to excreta, secreta, blood, blood components, tissue, and tissue fluids

Repository – Any collection of data or specimens

Registry - A list of individuals who have agreed to have their data (specimens or information) shared

Genetic Research – The use of genes and genetic material in research

Collection Protocol - The protocol that is used to establish the procedures for the collection of samples and data.

Management Protocol – The protocol that is used to manage the samples or data to be obtained under individual withdrawal studies.

Withdrawal Protocol – The protocol(s) that is used to withdraw samples or data from the storage bank.

Secondary use of de-identified data or samples – The additional use of data or samples that were obtained an IRB approved protocol and are now de-identified for any additional use.

Waste samples – Samples that would have been discarded.

## 18.4 Investigator Responsibilities

It is the responsibility of the investigator to determine the type or registry or repository as well as the minimum information necessary to meet the needs of the research.

If, during the design of the research, the investigator determines that the registry or repository was collected and maintained for non-research purposes then the investigator will need to provide documentation of the written authorization from the patient/research subject via a signed HIPAA waiver.

If the subject is unavailable or the research could not practicably be conducted, the investigator may request the approval of the DDEAMC IRB and the documentation of a formal waiver of the authorization requirement. The formal waiver requirements are outlined in later in this policy.

The last option for the investigator is the documentation that the research involves only one or more of the following:

a. Decedents' information – Submission to the DDEAMC IRB **is not required** as the human subject research regulations do not apply to deceased individuals.
b. De-identified information - Submission to the DDEAMC IRB **is required** for investigators whose research only involves de-identified information. The DDEAMC IRB will review the application to determine the applicability of the human subject research regulations and will notify the investigator via IRBNet.
c. Limited data sets or reviews preparatory to research –Submission to the DDEAMC IRB **is required** for studies involving only limited personal identifiers or for reviews preparatory to research. A data use agreement may be approved by the DDEAMC IRB so that the investigator may utilize a data-use agreement with the covered entity and/or repository to obtain the collected items. This highly restricted information is usually insufficient to conduct research. It is recommended for use in determining the feasibility of study as it relates to the number of subjects who may have a specific diagnosis.

Investigators should submit these for DDEAMC IRB review via IRBNet and should respond promptly to request for information from the DCI RRCO staff.

Each submission must address the following:

1. Purpose of the study and informing subjects that the data or biological sample that they provide will be used for research (such as genetic research on biological samples).
2. Inform the subjects of the storage of the data or biological sample:
    a. How long the data or biological sample will be stored
    b. Where the data or biological sample will be stored
    c. How the data or biological sample will be safeguarded
    d. Point of contact (POC) if retrieval or deletion of the data or biological sample becomes necessary (NOTE: It is appropriate to note that truly anonymous sample have no way of being identified if retrieval or deletion becomes necessary.)
3. Subject access to genetic information related to the data or biological sample:
    a. Inform the subjects what information regarding the results of the study that they will receive such as individual results or general summary of the group.
    b. State if the **results are not to be** provided.
    c. State if the **results are to be** provided and:
        i. Indicate at what point in the research that the findings will be disclosed
        ii. Describe who will be responsible for disseminating this information and the method of dissemination (i.e., return appointment, phone call, etc.)
        iii. Describe what supports are available after the subject is provided this information (i.e., genetic counseling, none applicable, etc.)
    d. Describe plans to handle incidental findings (paternity, disease or conditions other than the one under study for this particular research study).
4. Secondary use
    a. Inform subjects if subsequent investigators may be given access to samples
    b. If subsequent investigators will be given access to the samples, inform the subject whether the samples will be provided to the receiving investigators with or without identifiers.
    c. Give the subjects the option of consenting now to future second use.
    d. Disclose plans for future re-contact of the subjects.
    e. Describe plans for deciding priorities for future research projects involving the limited amount of tissue, as applicable.
    f. Describe a plan outlining who will control the decision regarding the use of these samples by other researchers.
5. Risks
    a. Inform the subject of any of the following applicable potential <u>social risks</u> that could be associated with learning the results of the research or a breach of confidentiality:
        i. Potential impacts on:
            1. Insurability
            2. Employability
            3. Reproduction plans
            4. Family relationships
            5. Immigration status
        ii. Potential for paternity suits
        iii. Potential for social stigmatization

   b. Inform the subject of any of the following applicable potential psychological risks that associated with learning the results of the research or a breach of confidentiality:
      i. Potential impacts on:
         1. Learning results
         2. Lack of existence of effective therapy
         3. Psychological stress for family members
   c. Inform the subject of any potential physical risks that associated with learning the results of the research or a breach of confidentiality
6. Confidentiality Issues
   a. Inform the subjects whether their identifiers will be maintained with the data or samples.
   b. If identifiers will be maintained, describe what identifiers will be maintained and detail the plan to keep research results and clinical identity separate.
   c. Describe plans for physical security of data and samples.
   d. Inform the subject about the limits of confidentiality (who will have access to the research results and under what circumstances). This should include the plan regarding access to the data by the subjects' family, third party payers, employers and the subjects' physician.
7. Costs to the subject
   Describe to the subject the cost of genetic counseling or psycho/social counseling that may be required if the results are disclosed.
8. Significant new findings
   Disclose the plan regarding willingness to inform subjects if, in the future, the research results are accepted to have clinical relevance.
9. Withdrawal from Research
   a. Inform the subject that they have the right to withdrawal and have the sample/data destroyed at any time.
   b. Inform the subject that they have the right to have identifiers removed without destroying the sample.
   c. Provide instructions regarding how to withdraw from the study or how to have identifiers removed.
10. Excess tissue protocols
   a. Inform the subjects that tissue removed from their body will be sent to pathology for diagnosis as established by hospital regulations.
      1. Include information regarding how it will be verified that surgically removed tissue is indeed excess tissue.
11. Family members
   a. If family members are involved in the research protocol, describe how each subject will be:
      i. Protected against disclosure of medical or other personal information about themselves to other family members.
      ii. Given the option not to receive information about themselves.
12. Commercial interest

a. Inform the subject about anyone having a commercial interest in the research (research team member, pharmaceutical or biotechnical company sponsor, or government agency).
b. Inform the subject that the samples they provide may have some commercial value and describe any financial benefit they may expect

## 18.5 DCI Research Regulatory Compliance Office (RRCO) Staff Responsibilities

The DCI RRCO is responsible for conducting an administrative review via IRBNet as outlined in Chapter 6 Policy #4 Exempt Review, Chapter 6 Policy #5 Expedited Review or Chapter 6 Policy #6 Convened Review, as applicable.

## 18.6 IRB Responsibilities

The DDEAMC IRB responsibilities will vary with the intent and the use of the registries or repositories. For example, if a registry or repository was created for purposes that are completely unrelated to research, then the IRB is **not** required to provide review, approval and oversight. These types of registries or repositories might include but are not limited to tracking the number of procedures that a resident might participate in for competency, billing marketing, quality control and public health surveillance. The DDEAMC IRB is not required to review research using samples or data from commercial or publicly available sources.

However, DDEAMC IRB approval is required for repositories for current or future research purposes. These types of registries or repositories must have research intent and are created, maintained/managed and operated for present or future research purposes. The future research purposes may be currently planned or they may not be currently known. The DDEAMC IRB review for both initial and continuing is required for these types of protocols. These are usually known as the collection or banking protocols. The DDEAMC IRB should also confirm that all protocols that will use genetic research involving human subjects that is conducted or supported by HHS has the appropriate Genetic Information Non-Discrimination Act (GINA) language in the informed consent as applicable.

The DDEAMC IRB approval is also required for each non-exempt study using data or specimens that were collected from the registry or repository. At times, a registry or repository that was created for non-research purposes will have someone who wishes to use that data or samples for research and IRB review is required for those types of protocols.

## 18.7 HIPAA Privacy Impact on the Research use of Data Registries or Specimen Repositories

The use of PHI in research or stored in non-research registries by DDEAMC or its MTFs under the covered Assurances cannot be used or disclosed for research unless the research use or research disclosure of PHI has obtained:

1. Written authorization from the subject; **or**
2. The approval of the DDEAMC IRB and the documentation of a formal waiver of the authorization requirement; **or**

3. Documents the HIPAA required representations from the investigator and determines that the research involves only one or more of the following:
    - Decedents' information
    - De-identified information
    - Limited data sets
    - Review preparatory to research.

It is reasonable for some data registries or sample repositories to have been collected prior to the thought of using the information for research purposes. Authorization for research purposes would not have been obtained from the individuals who provided the information or specimens to the non-research registry or repository since this was not the intent of the non-research registry or repository. This type of incident would require a waiver of authorization.

**Waiver of Authorization**

The DDEAMC IRB may approve this waiver of authorization if it determines and documents in IRBNet compliance with the DHHS regulations at 45 CFR 164.512(i)(2)(ii) that:

1) The use or disclosure of PHI involves no more than minimal risk to the privacy of individuals based on (at least) ALL of the following:
    a. An adequate plan to protect the identifiers from improper use and disclosure; **and**
    b. An adequate plan to destroy the identifiers at the earliest possible opportunity unless there is a research or a health justification for retaining them (or retention is required by law); **and**
    c. Adequate written assurances that the PHI will not be reused or disclosed to another person or entity (except as required by law, for authorized oversight of the research, etc.)
2) The research could not practicably be conducted without the alteration or waiver
3) The research could not practicably be conducted without access to and use of the PHI

## 18.8 References

The following references are provided for informational purposes:

1. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. December 28, 2001.
2. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2000.
3. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
4. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
5. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
6. Department of Defense Instruction 3216.02. Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research. November 8, 2011.
7. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
8. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.

9. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

**Resources regarding fetal tissue:**

10. OHRP Memo: Fetal Tissue Transplantation
http://www.hhs.gov/ohrp/humansubjects/guidance/fetal.html
11. Public Law: Research on Transplantation of Fetal Tissue
http://www.hhs.gov/ohrp/humansubjects/guidance/publiclaw103-43.htm

**Resources pertaining to identification of all subjects in the study:**

12. OHRP Decision Chart for Human Subject:
http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm#c1

**Resources pertaining to storage of biological specimens:**

13. OHRP Guidance Document: Issues to Consider in the Research Use of Stored Data or Tissues http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm
14. OHRP Guidance Document: Guidance on Research Involving Coded Private Information or Biological Specimens http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm
15. OHRP Guidance Document: Guidance on Certificates of Confidentiality
http://www.hhs.gov/ohrp/humansubjects/guidance/certconf.htm

**Resources regarding HIV Testing:**

16. OPRR Report: Policy on Informing Those Tested About HIV Serostatus
http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc88jun.htm
17. PHS Policy on Partner Notification
http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc90may.htm

# Chapter 19: Transnational Research

## 19.1 Purpose

The purpose of this policy is to provide direction for all transnational or international research conducted by any component of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC).

## 19.2 Background

While each culture is respected for its differences, the human subjects' protections must be equally applied and the research must be approved by their local equivalent of an institutional review board (IRB). The DDEAMC IRB serves as the IRB of record for the institution and any collaborative agreements must be in compliance with Chapter 11 Collaborative Agreements.

## 19.3 Definitions

**Transnational** – Composed of individuals or groups from different nationalities within a local population or across international borders.

## 19.4 IRB Responsibilities

The DDEAMC IRB must meet the basic IRB responsibilities as outlined earlier in the chapters as appropriate for the level of review. However, the addition of a transnational site does require additional responsibilities with the primary emphasis placed on knowledge of local context. Consultants may be necessary for the DDEAMC IRB to meet the requirement for knowledge of local context and their use is discussed in Chapter 6.

The Department of Health and Human Services (DHHS) Office for Human Research Protections provide general guidance on transnational research on and also offer the "International Compilation of Human Research Protections" as a resource for investigators and IRBs to use when determining human research protections.

## 19.5 Investigator Responsibilities

Each research team must become highly familiar with the pertinent laws, regulations and guidelines in the country where their research activities may take place. Issues that may require additional information are:

- Involvement of vulnerable populations
- Consistency between US regulations and the research site's conception of vulnerability
- Informed consent
    - Written versus oral languages
    - English translations and "back" translations
- Local standard of care options
- If a new treatment is offered during the course of the study but not after the study, how does that have an impact on the lives of the potential subjects?
- Other issues may be local norms (for example, privacy expectations)

The research team may be responsible for providing education to the local IRB and should work with the IRB to ensure that communication is as transparent as possible. All international sites conducting federally funded research must obtain an Assurance for International Institutions. Please contact the DCI RRCO for additional guidance.

It may also be required for the research team to identify appropriate consultants to the DDEAMC IRB.

## 19.6 DCI RRCO Responsibilities

The DCI RRCO must identify the transnational population and evaluate the previous experience of the DDEAMC IRB with this population to determine if consultants are needed to properly review the proposed research. If a consultant is necessary, the RRCO must identify the consultant. It may be required to contact the research team to assist in the identification of an appropriate consultant.

Translation services may be necessary for the informed consent form and other required documentation to ensure that subjects are able to understand the study as well as any requirements that they may have for their participation such as the completion of a survey, diary, etc.

## 19.7 Goals

The goal of the DCI RRCO is to gain knowledge about these types of protocols as there are currently very few in process at this organization.

## 19.8 References

The following references are provided for informational purposes:

1. Department of Health and Human Services (DHHS) Office for Human Research Protections, "International Compilation of Human Research Protections" available at http://www.hhs.gov/ohrp/international/HSPCompilation.pdf
2. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. December 28, 2001.
3. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2000.
4. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.
5. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
6. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
7. Department of Defense Instruction 3216.02. Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research. November 8, 2011.
8. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
9. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.

10. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.

# Chapter 20: Post Approval Compliance Monitoring/Audits for Quality Improvement and Compliance Monitoring

## 20.1 Purpose

The purpose of this policy is to provide direct guidance to any member of the Human Research Protection Program (HRPP) at the Dwight D. Eisenhower Army Medical Center (DDEAMC) who may be required to participate in a post approval compliance monitoring/audit for quality improvement and compliance monitoring of the research protocol.

## 20.2 Background

Each regulatory agency as well as funding sponsors have a responsibility to ensure that all research sites are compliant with federal regulations, state laws and when applicable, contractural obligations. An effective method to accomplish this responsibility is to conduct a post approval compliance monitoring/audit of the research team and their documentation.

There are several groups that may audit research involving human subjects. The Institutional Review Board (IRB) may be audited by Army Human Research Protection Office (AHRPO), Clinical Investigation Regulatory Office (CIRO), financial sponsors as well as the Department of Health and Human Services (DHHS OHRP), the Joint Commission (TJC), the Food and Drug Administration (FDA) and Office of the Secretary of Defense, Assistant Secretary of Defense for Health Affairs (HA).

Audits are the primary mechanism for ensuring compliance with the federal regulations that requires that IRBs confirm that no material changes have occurred in the research procedures since the previous IRB review. Investigators may be audited by the Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO), AHRPO, CIRO, financial sponsors as well as the FDA. Investigator sites who participate in clinical trials are usually monitored by the sponsor or contract research organization (CRO). These monitors are usually in turn audited by the sponsor to ensure that they are completing their contractural obligations. The DCI has a goal of conducting six audits per quarter. However, if a post approval compliance monitoring/audit reveals systemic violations and problems on specific study, then the goal may be adjusted to accommodate this information.

## 20.3 Definitions

**Audit** - An unbiased examination and evaluation of the documentation related to conduct of a research study. It can be done internally (by employees of the organization) or externally (by an outside firm). It is usually defined to a single time period.

**Monitor -** Watch closely for purposes of control, surveillance, etc. to ensure that good research practices are followed to ensure safety of the subject as well as compliance with applicable regulations and state law. This practice is usually ongoing during the life of the research.

**Sponsor -** A person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

**Contract Research Organization (CRO) -** A person [i.e., a legal person, which may be a corporation] that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration. [21 CFR 312.3(b)]

## 20.4 Audits of the HRPP including the IRB and DCI Research Regulatory Compliance Office (RRCO)

The IRB is responsible for maintaining documentation related to compliance with 32 CFR 319, 45 CFR 46, and 21 CFR 56. The IRB in its role as the Privacy Board is also responsible for compliance with HIPAA Privacy and Security Rules (45 CFR Parts 160 and 164). There are several federal regulatory agencies that may inspect HRPP and IRBs:

- Clinical Investigation Regulatory Office (CIRO)
- Army Human Research Protections Office (AHRPO)
- Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP)
- Office of the Secretary of Defense, Assistant Secretary of Defense for Health Affairs (HA)

### 20.4.1 CIRO or AHRPO Inspection of the DDEAMC IRB

The Department of Clinical Investigation (DCI) Research Regulatory Compliance Office (RRCO) should notify the following as soon as the site is notified of a post approval compliance monitoring/audit :

1. All DCI RRCO staff members
2. The Institutional Official (IO)
3. IRB members

This will assist the DCI RRCO in ensuring that all areas are ready to assist in the audit preparation and provide in-briefs and out-briefs to the Commander.

### 20.4.2 FDA Inspection of the IRB

**IRB Communication Responsibilities for FDA Audits**

The IRB should notify the following as soon as the site is notified of a post approval compliance monitoring/audit :

1. The DCI RRCO
2. The IO
3. CIRO
4. AHRPO IAW DoDI 3216.02, November 8, 2011, Enclosure 2, Section 3 (f) (6), of any notifications that the institution (DDEAMC) is under investigation for cause or for noncompliance with the applicable laws and regulations, including the Common Rule.

This will assist the IRB in ensuring that all areas are ready to assist in the audit preparation.

IRBs who review research studies for FDA regulated test articles must be prepared for an FDA audit. There are basically two types of FDA audits for IRBs:

1. Routine
2. For cause

The routine audits are the most common type of audits and are conducted every three (3) to five (5) years. The routine audit will usually be initiated by a phone call by the FDA inspector to determine a convenient time within two (2) weeks.

For cause audits are much more specific audits and are usually targeted to a specific study. These may result from a subject complaint, a potential whistleblower tip or if the study and/or site are highly publicized in the media. For cause audits will usually be initiated by an in person, non-scheduled visit by the FDA inspector.

The DDEAMC IRB is bound by the federal regulations to allow reasonable accommodations for all FDA inspectors and as such, cannot refuse an FDA inspection.

**FDA Timeframes**

It is important to note that the FDA can inspect the IRB during the conduct of a specific study and up to five (5) years post study completion. This is an additional incentive to fully document that activities related to the study. In the military environment, this becomes imperative due to frequent permanent change of station (PCS) moves of active duty military personnel and the current high operational tempo (OP TEMPO).

The FDA generally spends about three (3) to five (5) business days on each audit. However, the average amount of time that the FDA inspector conducts a post approval compliance monitoring/audit depends on several factors:

- Type of study
- Number of research studies selected for review
- Completeness and organization of required documentation

**Ways to Improve the Site**

Know the key players related to the conduct of the research and most importantly, know and understand the research study. Ensure that complete documentation exists for all IRB required items such as unanticipated problems, adverse event follow-up and protocol deviations or protocol violations. The documentation related to the study should be able to provide a concise and complete portrait of the conduct of the study.

**Prior to the Inspection**

Obtain a quiet room for the FDA Inspector that has adequate space, lighting, etc. and bring documents to the FDA Inspector upon their request. Assign a senior staff member to the FDA Inspector for their entire time at the site.

## During the Inspection

Upon the arrival of the FDA Inspector to the DDEAMC IRB, request to see the credentials (badge) of the FDA Inspector and the completed FDA Form 482: Notice of Inspection. A copy should be maintained of the FDA Form 482. Note that the FDA Inspector may ask to interview all staff and the staff should directly answer the questions honestly but no additional information should be volunteered.

The FDA Inspector will usually request the following documentation:

- A listing of all studies that fall under FDA regulations
- The IRB meeting minutes for the past year
- The IRB rosters for the past year
- Protocol specific files (NOTE: The FDA has generally determined that their inspectors will not access electronic systems for audits and as such printed documents must be available for their review.)

Make an inventory of all documents that the FDA Inspector requests and an additional copy of the documents to assist the site in the audit response to FDA. At the end of each day, it is customary for the FDA Inspector to meet with appropriate IRB staff members to address any issues that can be resolved as quickly as possible and prevent these unresolved issues from appearing in the audit report.

On the last day of the audit, the FDA Inspector will conduct an exit interview to discuss and clarify any findings. It is highly recommended that all IRB staff members attend the exit interviews. More than one staff member should take notes to assist in preparing the audit response, if applicable. This will also serve as an education and training exercise for quality improvement processes.

The FDA Inspector has the choice of two actions at the end of the audit:

1. Not issue a 483 as the site has no findings. NOTE: The FDA Inspector may require additional guidance from FDA Headquarters and the Form FDA 483 may be issued after this guidance takes place.
2. Issue a 483 which documents all inspection findings and deficiencies

If a Form FDA 483 is issued, then the IRB's response to FDA Form 483 must be completed by the site and submitted to the FDA Inspector. The FDA Inspector will prepare the Establishment Inspection Report (EIR) and submit this report along with the IRB's response to the FDA headquarters for their review. If the IRB's response is deemed adequate, the findings that correspond may be removed from the Form 483, in effect, not noted in the EIR and as such, are not officially noted in the EIR.

## After the FDA Audit

There are three types of action that the FDA may assign:

- No Action Indicated (NAI) – The research site is in compliance with FDA regulations. An acknowledgment letter will be sent to site and no response is required from the research site.

- Voluntary Action Indicated (VAI) – The FDA Inspector noted that there was an objectionable practice having minimal effect on study integrity (data or/or subject protections) noted. After FDA headquarters review, a formal letter is sent to the research site and response is required.
- Official Action Indicated (OAI) – The FDA Inspector noted objectionable conditions that require sanctions. This type of action requires immediate site response and action and increases the chance of a re-inspection.

The DDEAMC IRB response must be complete and prompt with involvement of the institutional official in the corrective action plan to ensure full support.

The FDA may issue a Warning Letter which signifies that the DDEAMC IRBs response to the FDA was an inadequate response. It also notes significant deficiencies requiring corrective action to avoid further regulatory action and implements a fifteen (15) day deadline for the response from the IRB outlining corrective actions. Examples of these letters are available on the FDA website and provide guidance on the FDA current inspection policies.

The FDA can also determine that the IRB non-response or continued non-compliance should result in disqualification, disbarment or prosecution.

### 20.4.3 DHHS OHRP Inspection of the IRB

**DCI RRCO Communication Responsibilities for DHHS OHRP Inspections**

The DCI RRCO should notify the following as soon as the site is notified of a post approval compliance monitoring/audit :

1. All DCI RRCO staff members
2. The IO
3. IRB members
4. CIRO
5. AHRPO IAW DoDI 3216.02, November 8, 2011, Enclosure 2, Section 3 (f) (6), of any notifications that the institution (DDEAMC) is under investigation for cause or for noncompliance with the applicable laws and regulations, including the Common Rule.

This will assist the DCI RRCO in ensuring that all areas are ready to assist in the audit preparation.

IRBs who review research studies covered under the federal wide assurance (FWA) for DHHS OHRP must be prepared for a DHHS OHRP audit. There are basically two types of DHHS OHRP audits for IRBs:
1. Not for cause
2. For cause

Not-for-cause compliance oversight evaluations are conducted in the absence of substantive allegations or indications of noncompliance. Institutions are selected for not-for-cause evaluation based on a range of considerations, including:

- The volume of HHS-conducted or -supported research in which they are engaged;
- Whether they have a history of a relatively low level of reporting to OHRP under the requirements of HHS regulations at 45 CFR 46.103(b)(5);
- The need to evaluate implementation of corrective actions following a previous for-cause compliance oversight evaluation;
- Geographic location;
- Status of accreditation by professionally recognized human subject protection program accreditation groups; and
- Status of recent human subject protection evaluations or audits by other regulatory agencies (such as the Food and Drug Administration) or recent participation in quality improvement programs (such as OHRP's Quality Improvement program).

For cause audits are in response to DHHS OHRP's receipt of substantive written allegations or indications of non-compliance with the DHHS regulations. Sources of such allegations or indications of noncompliance include, but are not limited to, research subjects and their family members, individuals involved in the conduct of research such as investigators and study coordinators, institutional officials, and research publications. The DHHS OHRP may choose to use other mechanisms to address allegations or indications of noncompliance rather than conducting a for-cause evaluation.

The full description of the DHHS OHRP audit process "OHRP's Compliance Oversight Procedures for Evaluating Institutions" is available on their website at http://www.hhs.gov/ohrp/compliance/ version date: October 14, 2009

The DDEAMC IRB is bound by the federal regulations to allow reasonable accommodations for all DHHS OHRP inspectors and as such, cannot refuse an inspection by DHHS OHRP.

**DHHS OHRP Timeframes**

It is important to note that the DHHS OHRP can inspect the DDEAMC IRB during the conduct of a specific study and up to five (5) years post-study completion. This is an additional incentive to fully document that activities related to the study. In the military environment, this becomes imperative due to permanent change of station PCS moves of active duty military personnel and the current high operational tempo (OP TEMPO).

The DHHS OHRP generally spends about three (3) to five (5) business days on each audit. However, the average amount of time that the FDA inspector conducts a post approval compliance monitoring/audit depends on several factors:

- Type of study
- Number of research studies selected for review
- Completeness of documentation
- Organization of documentation

**Ways to Improve the Site**

Promptly respond to the DHHS OHRP request and ensure that the response is factual, complete and can be substantiated through documentation and interviews.

## 20.5 Audits of the Investigator

There are several audits that the investigator may undergo but these are usually internal or external. Each audit type is discussed in detail in the sections that follow.

### 20.5.1 Internal Audits

#### Types and Causes of DCI RRCO Audits

The primary internal entity that will inspect investigators is the DCI RRCO. These audits are conducted to ensure that the researcher is in compliance with the DDEAMC IRB approved protocol. There are four (4) types of audits: self-audits, random, targeted and for cause. The self-audit may be requested only for no greater than minimal risks (NGTMR) research.

The criteria considered for selecting a study for a targeted audit are those studies:

- High risk or invasive procedures
- High volume subject enrollment
- Identified by the convened IRB as requiring continuing review more frequently than annually
- Multi-center trials

The criteria for selecting a study for a for cause audit are:

- Adverse events
    - Absence of reporting adverse events or
    - Large number of unexpected adverse events
- Identification of significant problems during continuing review
- Report of audit by appropriate authority
- Subject comment, concern, or complaint
- Whistleblowers

#### Notification of DCI RRCO Audit

The Principal Investigator (PI) is contacted by the DCI RRCO Senior Clinical Research Compliance Nurse and an appointment is scheduled. The goal is to schedule the audit within three (3) weeks to ensure a convenient time for the PI and the DCI RRCO Senior Clinical Research Compliance Nurse with their current responsibilities. The DCI RRCO Senior Clinical Research Compliance Nurse will provide an email notification confirming the date, time and location of the audit as well as the Self-Assessment Audit Checklist that will assist the PI in preparing for the audit. The Research monitor and/or research nurse/team members will be copied on the email and invited to attend, as applicable.

#### Audit Procedure

The type of audit will determine the audit procedures. If the audit is a random selection then the DCI RRCO Senior Clinical Research Compliance Nurse will conduct the audit and will contact the HPA, DCI, Chief; and DDEAMC IRB Chair for guidance and input as necessary. If the audit is for cause, then the DCI RRCO Senior Clinical Research Compliance Nurse will be accompanied by the HPA, DCI, Chief; or DDEAMC IRB Chair or a designee such as an experienced IRB member to assist in the audit. The DCI RRCO Senior Clinical Research Compliance Nurse will review the DDEAMC IRB file prior to meeting with the PI. The documentation noted below will be reviewed during the audit, as applicable, and may include other items specifically related to the research study, investigator site or study subject population

**Personnel/Research Team Member Documentation**

- Current list of personnel and delegated responsibilities on the appropriate form
- Signature and Responsibilities Log
- Contact Information
- Current Curriculum Vitae/ résumé and Medical Licenses for Laboratory Directors
- Current Curriculum Vitae (CV) or résumé for all research team members
- A copy of the most current professional license(s) for the appropriate research team member(s) (e.g., medical, nursing, pharmacist, etc.)
- Documentation of completion of initial mandatory CITI program for all research team members and recertification as applicable.
- Documentation of other education/training (i.e., Saf-T-Pak certification for the shipment of infectious materials) for all research team members and recertification as applicable.
- Financial Disclosure Forms, if applicable
- Investigator Agreement, if applicable
- Statement of Confidentiality, if applicable

**DDEAMC IRB Documentation**

- DDEAMC IRB Membership Rosters for the appropriate time points
- Original Protocol (sponsored and others) and subsequent amendments to include version dates and the DDEAMC Institutional Review Board (IRB) approval dates as documented by the DDEAMC IRB approval letter as well as the study specifics, which may include; inclusion/exclusion criteria, age of study participants, length of study, medications, etc.
- DDEAMC IRB requested changes and clarifications letter ( a.k.a. Stipulation letter) and letter of response from the Principal Investigator (PI)
- Initial approval letter from DDEAMC IRB
- Approval letters from other sites if applicable

**Laboratory Documentation**

- Copies of Laboratory Certifications for all labs used in the protocol
- Laboratory Normal Values for the study specific lab tests included in the protocol
- Impact statements and other organizational approvals such as the Radiation Safety Committee (RSC), as applicable

**Informed Consent Process - Recruitment Information to Informed Consent Forms/Child Assent Forms**

- Subject Screening Log
- Subject Enrollment Log
- Recruitment methods as described in the protocol.
- Advertisements and subsequent revisions to include the DDEAMC IRB approval dates as documented by the IRB approval letter
- Original Informed Consent Forms (ICF), Parental/Guardian Informed Consent Forms (P/GCF), and Children's Assent Forms (CAF)

**Amendments/Modifications**

- Nature and dates of all sponsor and non-sponsor amendments to the DDEAMC IRB approved protocol (e.g., changes in inclusion/exclusion criteria, study procedures, drug administration, research team members, etc.)
- Subsequent amendments of ICF, P/GCF, and CAF to include version dates and the DDEAMC IRB approval dates

**Continuing Review**

- Submission of the research protocol and investigators' requests for timely continuing review and approval by the DDEAMC IRB

**Reportable Events**

- Nature and dates of all Protocol Violations/Deviations
- Adverse event (AE) , unanticipated problems involving risks to subjects or others (UPIRSO), and serious adverse event (SAE) reports
- Deaths
- Data Safety Monitoring Board (DSMB) reports, if applicable
- Study Closure, Suspension or Termination

**Correspondence**

- DDEAMC IRB Correspondence
- Laboratory Correspondence
- General Correspondence
- Sponsor Correspondence, if applicable
- Contract Research Organization (CRO) Correspondence, if applicable
- Notification of Monitoring Visits, if applicable
- Monitoring Log, if applicable

**Additional Documentation for FDA Regulated Products**

- Form FDA 1572 and subsequent revisions, if applicable
- Drug/Device Accountability Log, if applicable
- Original Investigator's Brochure (Investigator's Drug Brochure, Clinical Investigator Brochure, Package Insert) and subsequent amendments to include version dates and the IRB approval dates as documented by the DDEAMC IRB approval letter
- Investigational New Drug (IND) Safety reports
- Study Status Updates from the Sponsor, if applicable

**Subject Files**

- ICF, P/GCF, CAF
- HIPAA Authorization Forms
- Data Collection Tools/Forms and/or Case Report Forms (CRFs)
- Source documents

The DCI RRCO Senior Clinical Research Compliance Nurse will review at least ten percent (10%) of the subjects enrolled in the study, or all of the records, if warranted. The individual records are selected by the auditor but will always include the first subject and the last subject enrolled. At the discretion of the auditor or the HRPP leadership, a one hundred percent (100%) audit may be conducted especially if there are less than five subjects enrolled or the complexity of the study. The research study subject records are audited to:

- Evaluate if the research data is organized, complete, and legible
- Verify that informed consent was obtained prior to the conduct of any study-related procedures including the review of the ICF, P/GCF and/or CAF for the following:
    - Initials of the research subject on each page of the ICF (excluding the signatory page)
    - Signature of the subject or the signature of the subject's legally authorized representative (LAR)
    - Signature of the investigator obtaining consent
    - Signature of a witness, if applicable
    - Dates written adjacent to each signature, in the hand of the signatory
    - Signatures are written in ink (if original)
    - Presence of the DDEAMC IRB release text box on the ICF along with the renewal date and the date of the most recent protocol revision
    - Utilization of the current version of the DDEAMC IRB approved ICF
    - Presence of any extemporaneous modification to the DDEAMC IRB approved ICF
    - Copy of the signed DDEAMC IRB approved scanned and filed in the subject's hospital medical record, if applicable
- Verify that the research subjects have met the inclusion and exclusion criteria
- Ascertain whether all pertinent study subject safety information (UPIRSO, SAE and AE) and research study procedures are being followed according to the protocol and to document protocol procedures not followed (e.g., specific study procedure not performed as required by the protocol) including documentation of study subjects enrolled in the research study who do not meet the inclusion and exclusion criteria
- Verify the DDEAMC IRB approved protocol was, and continues to be, followed appropriately (evaluate if the procedures performed on the research subject were items outlined in the IRB approved protocol and if there were any modifications to the study protocol implemented prior to being approved by the IRB)
- Verify that the information contained in the Case Report Forms (CRFs) or other data collection forms/tools were, or are, accurate and verifiable with source documentation

- Verify that the study drug, device, test article is stored, dispensed, and returned correctly and that appropriate study drug, device or test article accountability records are being maintained (if applicable)
- Verify the accountability records of the study device (if applicable)
- Verify lab results (if applicable)

**Elements of the Audit Review**
The DCI RRCO Audit Worksheet will be used during the audit of the subject's research record to assess adherence to the DDEAMC IRB approved protocol and applicable rules, regulations, and guidelines. There are several elements related to the audit review and are outlined below.

**Administrative Compliance**
- Copy of protocol and appropriate addenda
- Copy of protocol approval memorandum
- Copy of DDEAMC IRB Minutes granting approval
- Documentation of most current approved ICF
- All information pertaining to an investigational drug or device

**Protocol Compliance/Data Management**
- Evidence of:
    - Informed consent of the subjects enrolled in the study
    - Adhering to regulatory requirements
    - Compliance with DDEAMC IRB and their approval guidelines
    - Compliance with the DDEAMC HRPP
    - Protocol baseline studies and eligibility criteria
    - Disease status assessment
    - Documentation of:
        - Drug or device administration, if applicable
        - Drug or device distribution procedure, if applicable
        - Proper drug or device acquisition/dispensation record, if applicable
        - Equipment calibration reports, if applicable

**Reportable Events (UPIRSO, AEs, SAES, Deviations)**
- Copies of initial report of the reportable event
- Evidence of follow-up studies necessary to evaluate the effects of any adverse event
- Reports of procedural deviations
- Documentation of proper route of medication administration
- Evidence of correct dosing, timing or scheduling of procedures, or medication administration
- Evidence of dose adjustment in subjects with drug toxicity

**Treatment Comparisons/Interim Reporting**
- Reports of significant findings of treatment comparison
- Copies of continuing review and/or reports to the sponsor

**Audit Findings**
The DCI RRCO Senior Clinical Research Compliance Nurse or the audit team may reach any one of the following findings on each of the elements note above:

- No Deviations: No further action necessary but the audit team may share best practices
- Minor Deviations: Deviations that do not affect subject safety or the study outcome or interpretation.
- Major Deviations: Deviations from the critical elements stated above. These deviations could potentially affect subject safety, study outcome or interpretation.
- Unable to render a result at the time of the audit due to a lack of information.

**Reporting**

The Senior Clinical Research Compliance Nurse will conduct an exit interview with the PI after the audit is complete. This will include consultation on the audit findings and to clarify any issues that arose during the audit.

If there are deviations, the Senior Clinical Research Compliance Nurse will provide recommendations for correction to the PI and will submit such recommendations along with the audit report to the DDEAMC IRB for final determinations.

The final report with the findings noted will be distributed to the:

- PI along with the approximate date that the DDEAMC IRB will review the report
- Chief, DCI
- HPA
- DDEAMC IRB

**Corrective Actions**

The recommendations for correction made by the auditor to the PI will be submitted to the DDEAMC IRB for a decision. The Senior Clinical Research Compliance Nurse or the audit team will carry out any appropriate action or intervention determined by the IRB.

### 20.5.2 External Audits

There are several external entities that may inspect investigators:

- Food and Drug Administration (FDA)
- Sponsors and Contract Research Organizations (CRO)

**Investigator Communication Responsibilities**

The investigator and research team should notify the following as soon as the site is notified of a post approval compliance monitoring/audit :

1. The Human Protections Administrator (HPA)
2. The sponsor or CRO, if applicable
3. The funding agency, if applicable

4. The pharmacy, if applicable
5. Medical records, if applicable

This will assist the investigator in determining that all areas are ready to assist in the audit. If the study is closed, it will also allow these areas time to retrieve any required documentation.

**FDA Regulated Products**

Investigators who conduct research studies for FDA regulated test articles must be prepared for an FDA audit. There are three types of FDA audits:
1. Bioequivalent
2. Routine (study specific audit)
3. For cause (investigator specific audit)

Bioequivalent audits are usually the only site for a specific drug to be tested and as such as rare. These types of audits are usually determined in advance.

The routine audits are the most common type of audits and are usually directed by the study, not the individual investigator. The main triggers for these types of audits:
- High enrolling sites
- Pivotal trials
- Trials that will allow the status change from prescription only to over-the-counter (OTC) availability

The routine audit will usually be initiated by a phone call by the FDA inspector to determine a convenient time within two (2) weeks.

For cause audits are much more specific audits and are usually targeted to the specific investigator. These may result from a subject complaint, a potential whistleblower tip or if the site is highly publicized in the media. The FDA has additional concerns about an investigator who may conduct many studies or study outside their specialty or who conducts a pivotal study for a new drug application (NDA). The FDA usually becomes aware of these types of investigators when the safety and efficacy data submitted by the investigator is inconsistent with other research sites who are conducting the same research under the IND/IDE. An additional concern that the FDA may have is related to subject recruitment such as an unusually high number of potential subjects with a specific diagnosis to a geographical location without extensive documentation to support that claim.

For cause audits will usually be initiated by an in person, non-scheduled visit by the FDA Inspector.

Investigators and sponsors are bound by the federal regulations to allow reasonable accommodations for all FDA inspectors and as such, cannot refuse an FDA inspection.

**FDA Timeframes**

It is important to note that the FDA can inspect the research site during the conduct of the study and up to five (5) years post study completion. This is an additional incentive to fully document

that activities related to the study. In the military environment, this becomes imperative due to PCS and OP TEMPO.

The FDA generally spends about three (3) to five (5) business days on each audit. However, the average amount of time that the FDA inspector conducts a post approval compliance monitoring/audit depends on several factors:

- Type of study
- Number of subjects enrolled and completed
- Frequency of monitoring
- Completeness of documentation
- Organization of documentation

**Ways to Improve the Site**

Know the key players related to the conduct of the research and most importantly, know and understand the research study. Conduct a self-assessment of the regulatory documents and subject specific documentation. Ensure that complete documentation exists for all unanticipated problems, adverse event follow-up and protocol deviations or protocol violations. The documentation related to the study should be able to provide a concise and complete portrait of the conduct of the study.

**Prior to the Inspector Arrival**

Obtain a quiet room for the FDA Inspector that has adequate space, lighting, etc. Assign a senior staff member to the FDA Inspector for their entire time at the site.

**During the Inspection**

Make an inventory of all documents that the FDA Inspector requests and an additional copy of each document to assist the site in the audit response to FDA. At the end of each day, it is customary for the FDA Inspector to meet with appropriate research team members to address any issues that can be resolved as quickly as possible and prevent these unresolved issues from appearing in the audit report.

On the last day of the audit, the FDA Inspector will conduct an exit interview at to discuss and clarify any findings. It is highly recommended that all research team members attend the exit interviews and that more than one individual take notes to assist in preparing the audit response, if applicable, and to implement quality improvement processes for this and other research studies conducted by this team.

The FDA Inspector has the choice of two actions at the end of the audit – to not issue a 483 as the site has no findings or issue a completed Form FDA 483 which documents all inspection findings and deficiencies. The FDA Inspector may require additional guidance from FDA Headquarters and the Form FDA 483 may be issued after this guidance takes place.

If a Form FDA 483 is issued, then the Investigator's response to FDA Form 483 must be completed by the site and submitted to the FDA inspector. The FDA Inspector will prepare the

Establishment Inspection Report (EIR) and submit this report along with the Investigator's response to the FDA headquarters for their review. If the Investigator's response is deemed adequate, the findings that correspond may be removed from the Form 483, in effect, not noted in the EIR and as such, are not officially noted in the EIR.

### After the FDA Audit

There are three types of action that the FDA may assign:

- No Action Indicated (NAI) – The research site is in compliance with FDA regulations. An acknowledgment letter will be sent to site and no response is required from the research site.
- Voluntary Action Indicated (VAI) – The FDA Inspector noted that there was an objectionable practice having minimal effect on study integrity (data or/or subject protections) noted. After FDA headquarters review, a formal letter is sent to the research site and response is required.
- Official Action Indicated (OAI) – The FDA Inspector noted objectionable conditions that require sanctions. This type of action requires immediate site response and action and increases the chance of a re-inspection.

The Investigator Response should be complete and prompt. The DDEAMC IRB and the sponsor should be involved in the corrective action plan to ensure their full support.

The FDA may issue a Warning Letter which signifies that the Investigator response to the FDA was inadequate response. It also notes significant deficiencies requiring corrective action to avoid further regulatory action and implements a fifteen (15) day deadline for the response from the Investigator outlining corrective actions.

The FDA can also determine that the Investigator non-response or continued non-compliance should result in disqualification, disbarment or prosecution.

### Sponsors and Contract Research Organizations (CRO)

The sponsors and/or CROs routinely monitor the conduct of the study. At times, they may perform a post approval compliance monitoring/audit which may be a check of the performance of the study monitoring conduct by the CRO versus an actual investigator audit.

## 20.6 References

The following references are provided for informational purposes:

1. Army Regulation 40-7: Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances. January 4, 1991.
2. Army Regulation 40-38: Clinical Investigation Program. September 1, 1989.
3. Title 10 United States Code Section 980: Limitations on the use of humans as experimental subjects. January 7, 2011.
4. Title 32 Code of Federal Regulations (CFR) 219. Protection of Human Subjects. July 1, 2010.
5. Title 45 CFR 46. Protection of Human Subjects. Subparts A, B, C, D, E.

6. Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56 (as applicable).
7. Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
8. Department of Defense Directive 6025.18-R: DoD Health Information Privacy Regulation, January 2003
9. Department of Defense Instruction 3216.02. "*Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research*," November 8, 2011.
10. Department of Defense Directive 6200.2: Use of Investigational New Drugs for Force Health Protection. August 1, 2000.
11. Department of Defense Instruction 3210.7: Research Integrity and Misconduct. May 14, 2004.
12. 45 CFR §46.103(b)(4), 45 CFR §46.109, 45 CFR §46.116(b)(5), OHRP Guidance on Written Institutional Review Board (IRB) Procedures, OHRP Guidance on Continuing Review
13. Food and Drug Administration Regulations for the Protection of Human Subjects 21 CFR §50.25(b)(5), 21 CFR §56.108(a), 21 CFR §56.109, FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions: IRB Procedures
14. DCI Administrator Meeting, 25 March 2010, "Working together toward common understanding of regulatory compliance…AKA Getting CIRO off our back"
15. Email dated 12 February 2010 from COL Julie K. Zadinksy to Dr. Joseph Wood, subject line: Requested change in HLAR
16. Clinical Investigation Program (CIP) Educational Series, "The 7 in 111: Criteria for IRB Approval of Research Involving Human Subjects" Program Presentation by Ms. Caryn Duchesneau on 18 August 2010.
17. Bankert, EA, Amdur, RJ. Institutional Review Board Management and Function Second Edition. Jones and Bartlett; 2006.